

# ARTICLES



Preventing and  
recognizing  
prescription  
drug abuse  
See page 10.

## from the director:

The nonmedical use and abuse of prescription drugs is a serious public health problem in this country. Although most people take prescription medications responsibly, an estimated 52 million people (20 percent of those aged 12 and older) have used prescription drugs for nonmedical reasons at least once in their lifetimes. Young people are strongly represented in this group. In fact, the National Institute on Drug Abuse's (NIDA) Monitoring the Future (MTF) survey found that about 1 in 12 high school seniors reported past-year nonmedical use of the prescription pain reliever Vicodin in 2010, and 1 in 20 reported abusing OxyContin—making these medications among the most commonly abused drugs by adolescents.

The abuse of certain prescription drugs—opioids, central nervous system (CNS) depressants, and stimulants—can lead to a variety of adverse health effects, including addiction. Among those who reported past-year nonmedical use of a prescription drug, nearly 14 percent met criteria for abuse of or dependence on it. The reasons for the high prevalence of prescription drug abuse vary by age, gender, and other factors, but likely include greater availability.

The number of prescriptions for some of these medications has increased dramatically since the early 1990s (see figures, page 2). Moreover, a consumer culture amenable to “taking a pill for what ails you” and the perception of prescription drugs as less harmful than illicit drugs are other likely contributors to the problem. It is an urgent one: unintentional overdose deaths involving opioid pain relievers have quadrupled since 1999, and by 2007, outnumbered those involving heroin and cocaine.

NIDA hopes to change this situation by increasing awareness and promoting additional research on prescription drug abuse. Prescription drug abuse is not a new problem, but one that deserves renewed attention. It is imperative that as a Nation we make ourselves aware of the consequences associated with abuse of these medications.

Nora D. Volkow, M.D.  
Director  
National Institute on Drug Abuse

## Research Report Series

# Prescription Drugs: Abuse and Addiction



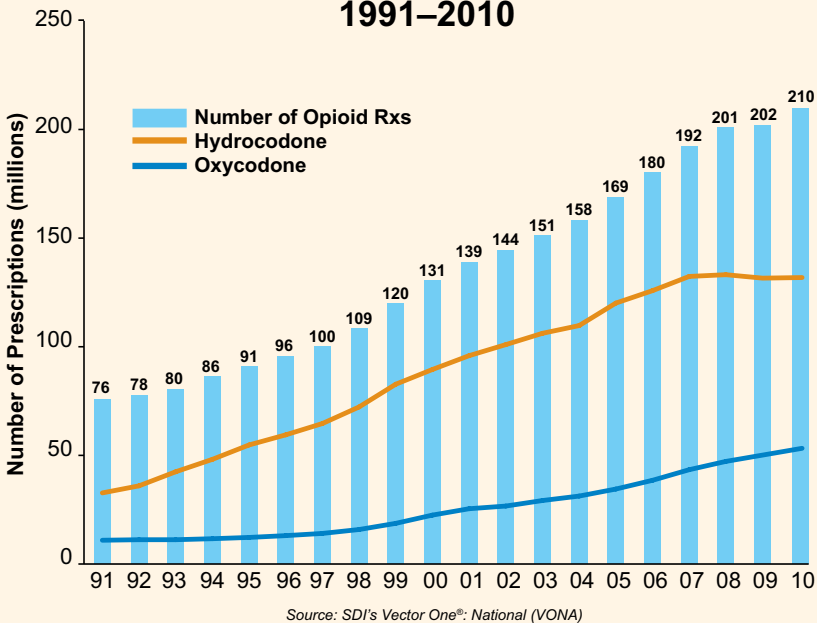
## What is prescription drug abuse?

**P**rescription drug abuse<sup>1</sup> is the use of a medication without a prescription, in a way other than as prescribed, or for the experience or feelings elicited. According to several national surveys, prescription medications, such as those used to treat pain, attention deficit disorders, and anxiety, are being abused at a rate second only to marijuana among illicit drug users. The consequences of this abuse have been steadily worsening, reflected in increased treatment admissions, emergency room visits, and overdose deaths.

*continued inside*

<sup>1</sup> Prescription drug abuse, as defined in this report, is equivalent to the term “nonmedical use,” used by many of the national surveys or data collection systems. This definition does not correspond to the definition of abuse/dependence listed in the Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV).

### Total Number of Opioid Prescriptions Dispensed by U.S. Retail Pharmacies, 1991–2010

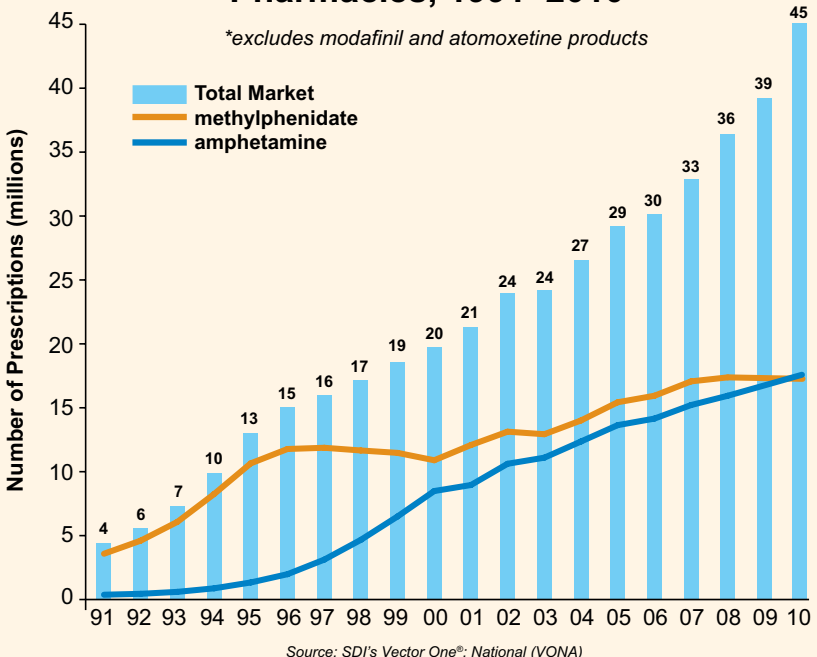


### What are some of the commonly abused prescription drugs?

Although many medications can be abused, the following three classes are most commonly abused:

- Opioids—usually prescribed to treat pain;
- Central nervous system (CNS) depressants—used to treat anxiety and sleep disorders; and
- Stimulants—most often prescribed to treat attention-deficit hyperactivity disorder (ADHD).

### Total Number of Prescriptions for Stimulants\* Dispensed by U.S. Retail Pharmacies, 1991–2010



### Opioids—

#### What are opioids?

Opioids are medications that relieve pain. They reduce the intensity of pain signals reaching the brain and affect those brain areas controlling emotion, which diminishes the effects of a painful stimulus. Medications that fall within this class include hydrocodone (e.g., Vicodin), oxycodone (e.g., OxyContin, Percocet), morphine (e.g., Kadian, Avinza), codeine, and related drugs. Hydrocodone products are the most commonly prescribed for a variety of painful conditions, including dental and injury-related pain. Morphine



is often used before and after surgical procedures to alleviate severe pain. Codeine, on the other hand, is often prescribed for mild pain. In addition to their pain-relieving properties, some of these drugs—codeine and diphenoxylate (Lomotil) for example—can be used to relieve coughs and severe diarrhea.

#### How do opioids affect the brain and body?

Opioids act by attaching to specific proteins called opioid receptors, which are found in the brain, spinal cord, gastrointestinal tract, and other organs in the body. When these drugs attach to their receptors, they reduce the perception of pain. Opioids can also produce drowsiness, mental confusion, nausea, constipation, and, depending

## Dependence vs. Addiction

Physical dependence occurs because of *normal* adaptations to chronic exposure to a drug and is not the same as addiction. Addiction, which can include physical dependence, is distinguished by compulsive drug seeking and use despite sometimes devastating consequences.

Someone who is physically dependent on a medication will experience withdrawal symptoms when use of the drug is abruptly reduced or stopped. These symptoms can be mild or severe (depending on the drug) and can usually be managed medically or avoided by using a slow drug taper.

Dependence is often accompanied by tolerance, or the need to take higher doses of a medication to get the same effect. When tolerance occurs, it can be difficult for a physician to evaluate whether a patient is developing a drug problem, or has a real medical need for higher doses to control their symptoms. For this reason, physicians need to be vigilant and attentive to their patients' symptoms and level of functioning to treat them appropriately.

upon the amount of drug taken, can depress respiration. Some people experience a euphoric response to opioid medications, since these drugs also affect the brain regions involved in reward. Those who abuse opioids may seek to intensify their experience by taking the drug in ways other than those prescribed. For example, OxyContin is an oral medication used to treat moderate to severe pain through a slow, steady release of the opioid. People who abuse OxyContin may snort or inject it,<sup>2</sup> thereby increasing their risk for serious medical complications, including overdose.

#### What are the possible consequences of opioid use and abuse?

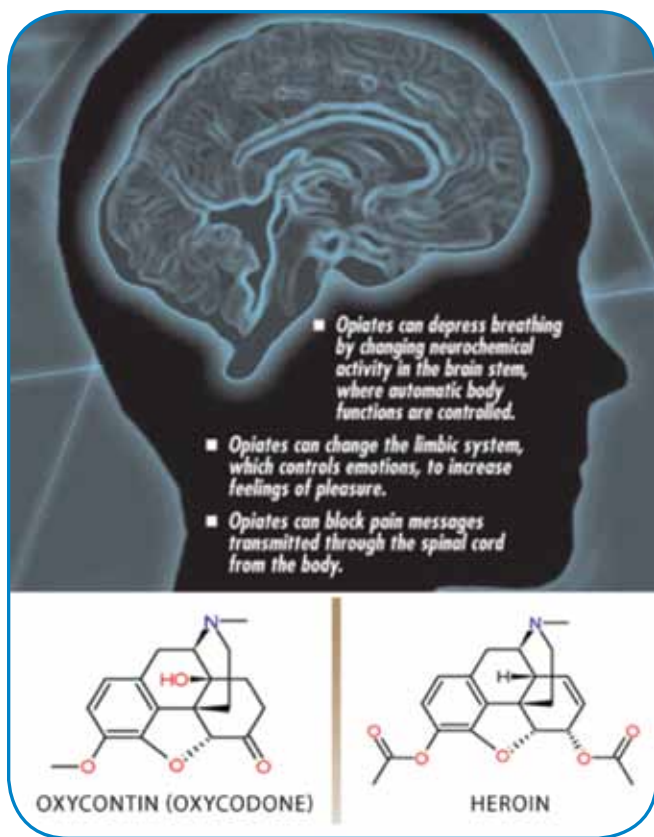
Taken as prescribed, opioids can be used to manage pain safely and effectively. However, when abused, even a single large dose can cause severe respiratory depression and death. Properly managed, short-term medical use of opioid analgesics rarely causes addiction—characterized by compulsive drug seeking and use despite serious adverse consequences. Regular (e.g., several times a day, for several weeks or more) or longer term use or abuse of opioids can lead to physical dependence and, in some cases,



***In 2007, the number of overdose deaths from prescription opioids outnumbered deaths from heroin and cocaine combined.***

<sup>2</sup> Changing the route of administration also contributes to the abuse of other prescription medications, including stimulants, a practice that can lead to serious medical consequences.





*OxyContin and heroin have similar chemical structures and bind to the same receptors in the brain.*

addiction. Physical dependence is a *normal* adaptation to chronic exposure to a drug and is not the same as addiction (see text box on “Dependence vs. Addiction” on page 3). In either case, withdrawal symptoms may occur if drug use

is suddenly reduced or stopped. These symptoms can include restlessness, muscle and bone pain, insomnia, diarrhea, vomiting, cold flashes with goose bumps (“cold turkey”), and involuntary leg movements.

## Over-the-Counter Medicines

Over-the-counter (OTC) medications, such as certain cough suppressants, sleep aids, and antihistamines, can be abused for their psychoactive effects. This typically means taking doses higher than recommended or combining OTC medications with alcohol, or with illicit or prescription drugs. Either practice can have dangerous results, depending on the medications involved. Some contain aspirin or acetaminophen (e.g., Tylenol), which can be toxic to the liver at high doses. Others, when taken for their “hallucinogenic” properties, can cause confusion, psychosis, coma, and even death.

Cough syrups and cold medications are the most commonly abused OTC medications. In 2010, for example, 6.6 percent of high school seniors took cough syrup “to get high.” At high doses, dextromethorphan—a key ingredient found in cough syrup—can act like PCP or ketamine, producing dissociative or out-of-body experiences.

## Is it safe to use opioid drugs with other medications?

Only under a physician’s supervision can opioids be used safely with other drugs. Typically, they should not be used with other substances that depress the CNS, such as alcohol, antihistamines, barbiturates, benzodiazepines, or general anesthetics, because these combinations increase the risk of life-threatening respiratory depression.

## CNS depressants—

### What are CNS depressants?

CNS depressants, sometimes referred to as sedatives and tranquilizers, are substances that can slow brain activity. This property makes them useful for treating anxiety and sleep disorders. Among the medications commonly prescribed for these purposes are the following:

- **Benzodiazepines**, such as diazepam (Valium) and alprazolam (Xanax), are sometimes prescribed to treat anxiety, acute stress reactions, and panic attacks. The more sedating benzodiazepines, such as triazolam (Halcion) and estazolam (ProSom) are prescribed for short-term treatment of sleep disorders. Usually, benzodiazepines are not prescribed for long-term use because of the risk for developing tolerance, dependence, or addiction.

- **Non-benzodiazepine sleep medications**, such as zolpidem (Ambien), eszopiclone (Lunesta), and zalepon (Sonata), have a different chemical structure, but act on some of the same brain receptors as benzodiazepines. They are thought to have fewer side effects and less risk of dependence than benzodiazepines.
- **Barbiturates**, such as mephobarbital (Mebaral), phenobarbital (Luminal Sodium), and pentobarbital sodium (Nembutal), are used less frequently to reduce anxiety or to help with sleep problems because of their higher risk of overdose compared to benzodiazepines. However, they are still used in surgical procedures and for seizure disorders.

#### How do CNS depressants affect the brain and body?

Most CNS depressants act on the brain by affecting the neurotransmitter gamma-aminobutyric acid (GABA). Neurotransmitters are brain chemicals that facilitate communication between brain cells. Although the different classes of CNS depressants work in unique ways, it is through their ability to increase GABA—and thereby inhibit brain activity—that they produce a drowsy or calming effect beneficial to those suffering from anxiety or sleep disorders.



#### What are the possible consequences of CNS depressant use and abuse?

Despite their many beneficial effects, benzodiazepines and barbiturates have the potential for abuse and should be used only as prescribed. The use of non-benzodiazepine sleep aids is less well studied, but certain indicators have raised concern about their abuse liability as well. During the first few days of taking a prescribed CNS depressant, a person usually feels sleepy and uncoordinated, but as the body becomes accustomed to the effects of the drug and tolerance develops, these side effects begin to disappear. If one uses these drugs long term, larger doses may be needed to achieve the therapeutic effects. Continued use can also lead to physical dependence and withdrawal when use is abruptly reduced or stopped (see text box on “Dependence vs. Addiction” on page 3). Because all CNS depressants work by slowing the brain’s activity, when

an individual stops taking them, there can be a rebound effect, resulting in seizures or other harmful consequences. Although withdrawal from benzodiazepines can be problematic, it is rarely life threatening, whereas withdrawal from prolonged use of barbiturates can have life-threatening complications. Therefore, someone who is thinking about discontinuing CNS depressant therapy or who is suffering withdrawal from a CNS depressant should speak with a physician or seek immediate medical treatment.

#### Is it safe to use CNS depressants with other medications?

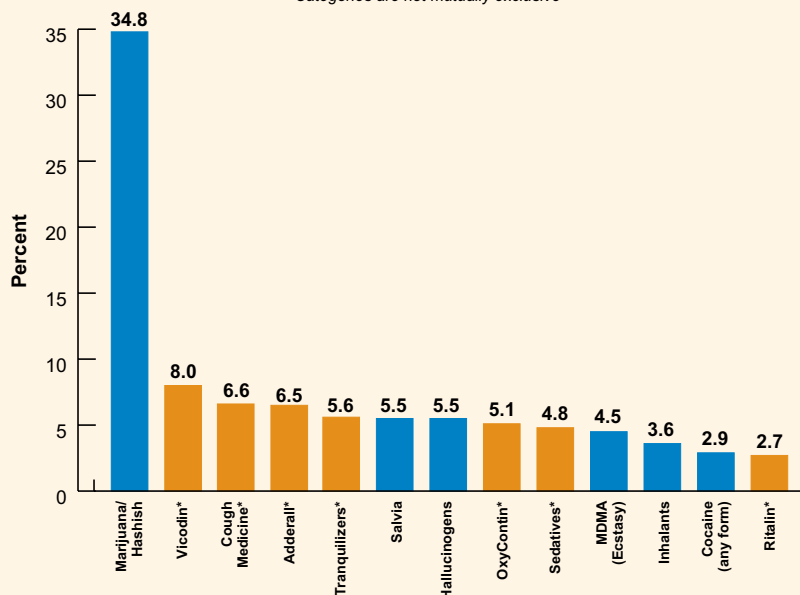
Only under a physician’s supervision is it safe to use CNS depressants with other medications. Typically, they should not be combined with any other medication or substance that causes CNS depression, including prescription pain medicines, some OTC cold and allergy medications, and alcohol. Using CNS depressants with these other substances—particularly alcohol—can affect heart rhythm, slow respiration, and even lead to death.



## After Marijuana, Prescription and Over-the-Counter Medications\* Account for Most of the Commonly Abused Drugs

Prevalence of Past-Year Drug Use Among 12th Graders

Categories are not mutually exclusive



SOURCE: University of Michigan, 2010 Monitoring the Future Study

\* Nonmedical Use

only a few health conditions, including ADHD, narcolepsy, and occasionally depression—in those who have not responded to other treatments.

### How do stimulants affect the brain and body?

Stimulants, such as dextroamphetamine (Dexedrine and Adderall) and methylphenidate (Ritalin and Concerta), act in the brain similarly to a family of key brain neurotransmitters called monoamines, which include norepinephrine and dopamine. Stimulants enhance the effects of these chemicals in the brain. The associated increase in dopamine can induce a feeling of euphoria when stimulants are taken nonmedically. Stimulants also increase blood pressure and heart rate, constrict blood vessels, increase blood glucose, and open up breathing passages.

## Stimulants—

### What are stimulants?

As the name suggests, stimulants increase alertness, attention, and energy, as well as elevate blood pressure, heart rate, and respiration. Stimulants historically were used to treat asthma and other respiratory problems, obesity, neurological disorders, and a variety of other ailments. But as their potential for abuse and addiction became apparent, the medical use of stimulants began to wane. Now, stimulants are prescribed to treat

## Cognitive Enhancers

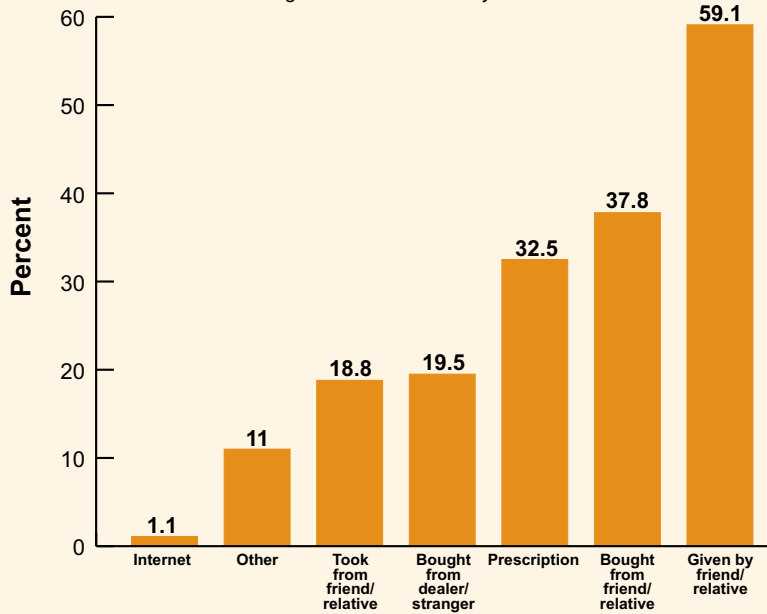
The dramatic increases in stimulant prescriptions over the last 2 decades have led to their greater environmental availability and increased risk for diversion and abuse. For those who take these medications to improve properly diagnosed conditions, they can be transforming, greatly enhancing a person's quality of life. However, because they are perceived by many to be generally safe and effective, prescription stimulants, such as Concerta or Adderall, are increasingly being abused to address nonmedical conditions or situations. Indeed, reports suggest that the practice is occurring among some academic professionals, athletes, performers, older people, and both high school and college students. Such nonmedical cognitive enhancement poses potential health risks, including addiction, cardiovascular events, and psychosis.



**Youth who abuse prescription medications are also more likely to report use of other drugs.**

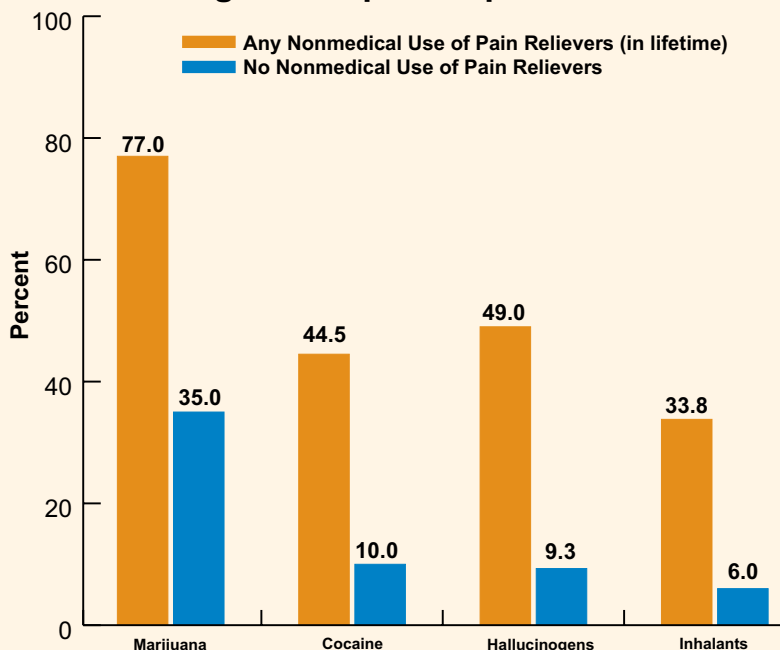
## Source of Prescription Narcotics among Those Who Used in the Past-Year, 12th Grade\*

\* Categories are not mutually exclusive



SOURCE: University of Michigan, 2010 Monitoring the Future Study

## Greater Lifetime Use of Illicit Drugs among Prescription Opiate Abusers



The rate of use of other drugs is significantly higher among those who have abused prescription drugs in their lifetimes. The same is true for past-year users.

SOURCE: SAMHSA. Misuse of prescription drugs: Data from the 2002, 2003, and 2004 National Surveys on Drug Use and Health. HHS Pub. No. (SMA)06-4192. Rockville, MD: Office of Applied Studies, 2006.

## What are the possible consequences of stimulant use and abuse?

As with other drugs of abuse, it is possible for individuals to become dependent upon or addicted to stimulants. Withdrawal symptoms associated with discontinuing stimulant use include fatigue, depression, and disturbance of sleep patterns. Repeated abuse of some stimulants (sometimes within a short period) can lead to feelings of hostility or paranoia, even psychosis. Further, taking high doses of a stimulant may result in dangerously high body temperature and an irregular heartbeat. There is also the potential for cardiovascular failure or seizures.

## Is it safe to use stimulants with other medications?

Stimulants should not be used with other medications unless authorized by a physician. Patients also should be aware of the dangers associated with mixing stimulants and OTC cold medicines that contain decongestants, as combining these substances may cause blood pressure to become dangerously high or lead to irregular heart rhythms.

## Trends in prescription drug abuse

### How many people abuse prescription drugs?

According to results from the 2010 National Survey on Drug Use and Health (NSDUH), an estimated 2.4 million Americans used prescription drugs nonmedically for the first time within the past year,



which averages to approximately 6,600 initiates per day. More than one-half were females and about a third were aged 12 to 17. Although prescription drug abuse affects many Americans, certain populations, such as youth, older adults, and women, may be at particular risk.

#### Adolescents and young adults

Abuse of prescription drugs is highest among young adults aged 18 to 25, with 5.9 percent reporting nonmedical use in the past month (NSDUH, 2010). Among youth aged 12 to 17, 3.0 percent reported past-month nonmedical use of prescription medications.

According to the 2010 MTF, prescription and OTC drugs are among the most commonly abused drugs by 12th graders (see figure on page 6), after alcohol, marijuana, and tobacco. While past-year nonmedical use of sedatives and tranquilizers decreased among 12th graders over the last 5 years, this is not the case for the nonmedical use of amphetamines or opioid pain relievers.

When asked how prescription opioids were obtained for nonmedical use, more than half of the 12th graders surveyed said they were given the drugs or bought them from a friend or



relative. Interestingly, the number of students who purchased opioids over the Internet was negligible (see top chart on previous page).

Youth who abuse prescription medications are also more likely to report use of other drugs. Multiple studies have revealed associations between prescription drug abuse and higher rates of cigarette smoking; heavy episodic drinking; and marijuana, cocaine, and other illicit drug use among adolescents, young adults, and college students in the United States (see bottom chart on previous page).

#### Older adults

Persons aged 65 years and older comprise only 13 percent of the population, yet account for more than one-third of total outpatient spending on prescription medications in the United States. Older patients are more likely to be prescribed long-term and multiple prescriptions, and some experience cognitive decline, which could lead to improper use of medications. Alternatively, those on a fixed income may abuse another person's remaining medication to save money.

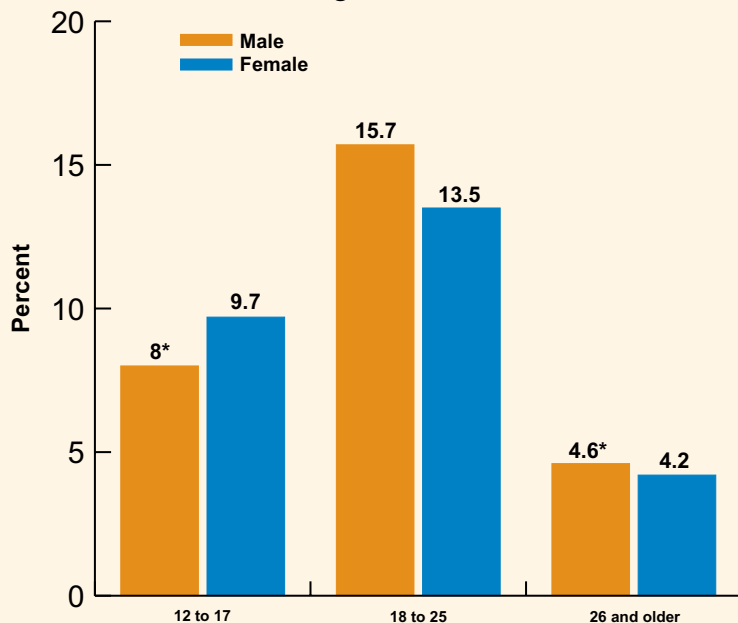
The high rates of comorbid illnesses in older populations, age-related changes in drug metabolism, and the potential for drug interactions may make any of these practices more dangerous than in younger populations. Further, a large percentage of older adults also use OTC medicines and dietary supplements, which (in addition to alcohol) could compound any adverse health consequences resulting from prescription drug abuse.



***Older patients are more likely to be prescribed long-term and multiple prescriptions, which could lead to improper use of medications.***

### Past-Year Nonmedical Use of Psychotherapeutics Among Persons 12 or Older, by Gender and Age Group

Annual averages based on 2002-2005



\* Difference from male to female significant at  $p < 0.01$ .

SOURCE: Cotto, J.H., et al. Gender effects on drug use, abuse, and dependence: An analysis of results from the National Survey on Drug Use and Health. *Gen Med* 7(5):402-413, 2010.

### Gender differences

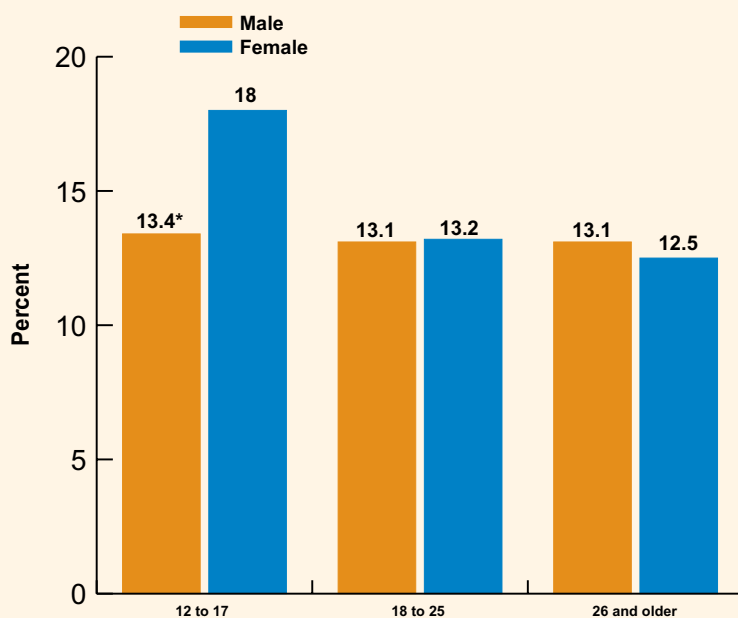
Overall, more males than females abuse prescription drugs in all age groups except the youngest (aged 12 to 17 years); that is, females in this age group exceed males in the nonmedical use of *all* psychotherapeutics, including pain relievers, tranquilizers, and stimulants. Among *nonmedical users* of prescription drugs, females 12 to 17 years old are also more likely to meet abuse or dependence criteria for psychotherapeutics (see figure, left).

### How many people suffer adverse health consequences from abusing prescription drugs?

The Drug Abuse Warning Network (DAWN), which monitors emergency department (ED) visits in selected areas across the Nation, reported that approximately 1 million ED visits in 2009 could be attributed to prescription drug abuse. Roughly 343,000 involved prescription opioid pain relievers, a rate more than double that of 5 years prior. ED visits also more than doubled for CNS stimulants, involved in nearly 22,000 visits in 2009, as well as CNS depressants (anxiolytics, sedatives, and hypnotics), involved in 363,000 visits. Of the latter, benzodiazepines (e.g., Xanax) comprised the vast majority. Rates for a popular prescribed non-benzodiazepine sleep aid, zolpidem (Ambien), rose from roughly 13,000 in 2004 to 29,000 in 2009. More than half of ED visits for prescription drug abuse involved multiple drugs.

### Past-Year Dependence or Abuse of Psychotherapeutics Among Past-Year Nonmedical Users 12 or Older, by Gender and Age Group

Annual averages based on 2002-2005



\* Difference from male to female significant at  $p < 0.01$ .

SOURCE: Cotto, J.H., et al. Gender effects on drug use, abuse, and dependence: An analysis of results from the National Survey on Drug Use and Health. *Gen Med* 7(5):402-413, 2010.



*To ensure proper medical care, patients should discuss any and all drug use—including prescription and over-the-counter medications—with their doctors.*

## Preventing and recognizing prescription drug abuse

The risks for addiction to prescription drugs increase when they are used in ways other than as prescribed (e.g., at higher doses, by different routes of administration, or combined with alcohol or other drugs). Physicians, their patients, and pharmacists all can play a role in identifying and preventing prescription drug abuse.

**Physicians.** More than 80 percent of Americans had contact with a healthcare professional in the past year, placing doctors in a unique position, not only to prescribe medications, but also to identify abuse (or nonmedical use) of prescription drugs and prevent the escalation to addiction. By asking about *all* drugs, physicians can help their patients recognize that a problem exists, set recovery goals, and seek appropriate treatment. Screening for prescription drug abuse can be incorporated into routine medical

visits. Doctors should also take note of rapid increases in the amount of medication needed or frequent, unscheduled refill requests. Doctors should be alert to the fact that those addicted to prescription drugs may engage in “doctor shopping”—moving from provider to provider—in an effort to obtain multiple prescriptions for the drug(s) they abuse.

Preventing or stopping prescription drug abuse is an important part of patient care. However, healthcare providers should not avoid prescribing stimulants, CNS depressants, or opioid pain relievers if needed. (See text box on “Chronic Pain Treatment and Addiction” on page 13.)

**Patients.** For their part, patients can take steps to ensure that they use prescription medications appropriately: always follow the prescribed directions, be aware of potential interactions with other drugs, never stop or change a dosing regimen without first discussing it with a healthcare provider, and never use another person’s prescription. In addition to describing their medical problem, patients should always inform their healthcare professionals about all the prescriptions, OTC medicines, and dietary and herbal supplements they are taking, before they obtain any other medications. Additionally, unused or expired medications should be properly



***Prescription Drug Monitoring Programs allow physicians and pharmacists to track prescriptions and help identify patients who are “doctor shopping.”***

discarded per U.S. Food and Drug Administration (FDA) guidelines or at U.S. Drug Enforcement Administration collection sites.

**Pharmacists.** Pharmacists dispense medications and can help patients understand instructions for taking them. By being watchful for prescription falsifications or alterations, pharmacists can serve as the first line of defense in recognizing prescription drug abuse. Some pharmacies have developed hotlines to alert other pharmacies in the region when a fraudulent prescription is detected. Moreover, prescription drug monitoring programs (PDMPs), which require physicians and pharmacists to log each filled prescription into a State database, can assist medical professionals in identifying patients who are getting prescriptions from multiple sources. As of May 2011, 48 States and 1 territory have enacted legislation authorizing PDMPs, 34 of which are operational.

## Treating prescription drug addiction

Years of research have shown that addiction to any drug (illicit or prescribed) is a brain disease that can be treated effectively. Treatment must take into account the type of drug used and the needs of the individual. Successful treatment may need to incorporate several components, including detoxification, counseling, and sometimes the use of addiction medications. Multiple courses of treatment may be needed for the patient to make a full recovery.



*Although a behavioral or pharmacological approach alone may be sufficient for treating some patients, research shows that a combined approach may be best.*

The two main categories of drug addiction treatment are behavioral and pharmacological. Behavioral treatments help patients stop drug use by teaching them strategies to function without drugs, deal with cravings, avoid drugs and situations that could lead to drug use, and handle a relapse should it occur. When delivered effectively, behavioral treatments, such as individual counseling, group or family counseling, contingency management, and cognitive-behavioral therapies, also can help patients improve their personal relationships and their ability to function at work and in the community.

Some addictions, such as opioid addiction, can be treated with medications. These pharmacological treatments counter the effects of the drug on the brain and behavior, and

can be used to relieve withdrawal symptoms, help overcome drug cravings, or treat an overdose. Although a behavioral or pharmacological approach alone may be sufficient for treating some patients, research shows that a combined approach may be best.

### Treating addiction to prescription opioids

Several options are available for effectively treating prescription opioid addiction. These options are drawn from research on the treatment of heroin addiction and include medications (e.g., naltrexone, methadone, and buprenorphine) as well as behavioral counseling approaches.

Naltrexone is an *antagonist* medication that prevents opioids from activating their receptors. It is used to treat overdose and addiction, although its use for addiction has been limited due to





poor adherence and tolerability by patients. Recently, an injectable, long-acting form of naltrexone (Vivitrol), originally approved for treating alcoholism, has also received FDA approval to treat opioid addiction (i.e., heroin or other opioids). Because its effects last for weeks, Vivitrol is ideal for patients who do not have ready access to healthcare or who struggle with taking their medications regularly. Methadone is a synthetic opioid *agonist* that eliminates withdrawal symptoms and relieves drug cravings by acting on the same brain targets as other opioids like heroin, morphine, and opioid pain medications. It has been used successfully for more than 40 years to treat heroin addiction, but must be dispensed through opioid treatment programs. Buprenorphine is a partial opioid agonist (i.e., it has agonist and antagonist properties), which can be prescribed by certified physicians in an office setting. Like methadone, it

can reduce cravings and is well tolerated by patients. NIDA is supporting research needed to determine the effectiveness of these medications in treating addiction to opioid pain relievers.

#### **Treating addiction to CNS depressants**

Patients addicted to barbiturates and benzodiazepines should not attempt to stop taking them on their own. Withdrawal symptoms from these drugs can be problematic, and—in the case of certain CNS depressants—potentially life-threatening. Research on treating barbiturate and benzodiazepine addiction is sparse; however, addicted patients should undergo medically supervised detoxification because the dosage they take should be gradually tapered. Inpatient or outpatient counseling can help individuals through this process. Cognitive-behavioral therapy, which focuses on modifying the patient's thinking,

expectations, and behaviors while increasing skills for coping with various life stressors, also has been used successfully to help individuals adapt to discontinuing benzodiazepines.

Often barbiturate and benzodiazepine abuse occurs in conjunction with the abuse of other drugs, such as alcohol or cocaine. In such cases of polydrug abuse, the treatment approach should address the multiple addictions.

#### **Treating addiction to prescription stimulants**

Treatment of addiction to prescription stimulants, such as Adderall and Concerta, is based on behavioral therapies used in treating cocaine and methamphetamine addiction. At this time, there are no medications that are FDA-approved for treating stimulant addiction. Thus, NIDA is supporting research in this area.

Depending on the patient's situation, the first steps in treating prescription stimulant addiction may be to taper the drug dosage and attempt to ease withdrawal symptoms. The detoxification process could then be followed by behavioral therapy. Contingency management, for example, uses a system that enables patients to earn vouchers for drug-free urine tests. (These vouchers can be exchanged for items that promote healthy living.) Cognitive-behavioral therapy also may be an effective treatment for addressing stimulant addiction. Finally, recovery support groups may be helpful in conjunction with behavioral therapy.

## Chronic Pain Treatment and Addiction

Healthcare providers have long wrestled with how best to treat patients who suffer from chronic pain, roughly 116 million in this country. Their dilemma stems from the potential risks involved with long-term treatment, such as the development of drug tolerance (and the need for escalating doses), hyperalgesia (increased pain sensitivity), and addiction. Patients themselves may even be reluctant to take an opioid medication prescribed to them for fear



of becoming addicted. Estimates of addiction among chronic pain patients vary widely—from about 3 percent to 40 percent. This variability is the result of differences in treatment duration, insufficient research on long-term outcomes, and disparate study populations and measures used to assess abuse or addiction.

To mitigate addiction risk, physicians should screen patients for potential risk factors, including personal or family history of drug abuse or mental illness. Monitoring patients for signs of abuse is also crucial, and yet some indicators can signify multiple conditions, making accurate assessment challenging. Early or frequent requests for prescription pain medication refills, for example, could represent illness progression, the development of drug tolerance, or the emergence of a drug problem.

The development of effective, nonaddicting pain medications is a public health priority. A growing elderly population and an increasing number of injured military only add to the urgency of this issue. Researchers are exploring alternative medications that can alleviate pain but have less abuse potential. More research is needed to better understand effective chronic pain management, including identifying factors that predispose some patients to addiction and developing measures to prevent abuse.

## Glossary

**Addiction:** A chronic, relapsing disease characterized by compulsive drug seeking and use, despite serious adverse consequences, and by long-lasting changes in the brain.

**Agonist:** A chemical entity that binds to a receptor and activates it, mimicking the action of the natural (or abused) substance that binds there.

**Antagonist:** A chemical entity that binds to a receptor and blocks its activation. Antagonists prevent the natural (or abused) substance from activating its receptor.

**Barbiturate:** A type of CNS depressant prescribed to promote sleep (usually in surgical procedures) or as an anticonvulsant.

**Benzodiazepine:** A type of CNS depressant prescribed to relieve anxiety and sleep problems. Valium and Xanax are among the most widely prescribed medications.

**Buprenorphine:** A mixed opiate agonist/antagonist medication approved by the FDA in October 2002 for the treatment of opioid addiction (e.g., heroin).

**Central Nervous System:** The brain and spinal cord.

**CNS Depressants:** A class of drugs that slow CNS function (also called sedatives and tranquilizers), some of which are used to treat anxiety and sleep disorders; includes barbiturates and benzodiazepines.

**Comorbidity:** The occurrence of two disorders or illnesses in the same person, also referred to as co-occurring conditions or dual diagnosis. Patients with comorbid illnesses may experience a more severe illness course and require treatment for each or all conditions.

**Detoxification:** A process in which the body rids itself of a drug (or its metabolites). During this period, withdrawal symptoms can emerge that may require medical treatment. This is often the first step in drug abuse treatment.

**Dopamine:** A brain chemical, classified as a neurotransmitter, found in regions that regulate movement, emotion, motivation, and pleasure.

**Methadone:** A long-acting synthetic opioid medication that is effective in treating opioid addiction and pain.

**Narcolepsy:** A disorder characterized by uncontrollable episodes of deep sleep.

**Norepinephrine:** A neurotransmitter present in the brain and the peripheral (sympathetic) nervous system; and a hormone released by the adrenal glands. Norepinephrine is involved in attention, responses to stress, and it regulates smooth muscle contraction, heart rate, and blood pressure.

**Opioid:** A compound or drug that binds to receptors in the brain involved in the control of pain and other functions (e.g., morphine, heroin, hydrocodone, oxycodone).

**Physical Dependence:** An adaptive physiological state that occurs with regular drug use and results in a withdrawal syndrome when drug use is stopped; often occurs with tolerance. Physical dependence can happen with chronic—even appropriate—use of many medications, and by itself does not constitute addiction.

**Polydrug Abuse:** The abuse of two or more drugs at the same time, such as CNS depressants and alcohol.

**Prescription Drug Abuse:** The use of a medication without a prescription; in a way other than as prescribed; or for the experience or feeling elicited. This term is used interchangeably with “nonmedical” use, a term employed by many of the national surveys.

**Psychotherapeutics:** Drugs that have an effect on the function of the brain and that often are used to treat psychiatric/neurologic disorders; includes opioids, CNS depressants, and stimulants.

**Respiratory Depression:** Slowing of respiration (breathing) that results in the reduced availability of oxygen to vital organs.

**Sedatives:** Drugs that suppress anxiety and promote sleep; the NSDUH classification includes benzodiazepines, barbiturates, and other types of CNS depressants.

**Stimulants:** A class of drugs that enhances the activity of monoamines (such as dopamine) in the brain, increasing arousal, heart rate, blood pressure, and respiration, and decreasing appetite; includes some medications used to treat attention-deficit hyperactivity disorder (e.g., methylphenidate and amphetamines), as well as cocaine and methamphetamine.

**Tolerance:** A condition in which higher doses of a drug are required to produce the same effect achieved during initial use; often associated with physical dependence.

**Tranquilizers:** Drugs prescribed to promote sleep or reduce anxiety; the NSDUH classification includes benzodiazepines, barbiturates, and other types of CNS depressants.

**Withdrawal:** Symptoms that occur after chronic use of a drug is reduced abruptly or stopped.



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## Where Can I Get More Scientific Information on Prescription Drug Abuse?

To learn more about prescription drugs and other drugs of abuse, or to order materials on these topics free of charge in English or Spanish, visit the NIDA Web site at [www.drugabuse.gov](http://www.drugabuse.gov) or contact the *DrugPubs* Research Dissemination Center at 877-NIDA-NIH (877-643-2644; TTY/TDD: 240-645-0228).



### What's New on the NIDA Web Site

- Information on drugs of abuse
- Publications and communications (including *NIDA Notes* and *Addiction Science & Clinical Practice journal*)
- Calendar of events
- Links to NIDA organizational units
- Funding information (including program announcements and deadlines)
- International activities
- Links to related Web sites (access to Web sites of many other organizations in the field)

### NIDA Web Sites

[drugabuse.gov](http://drugabuse.gov)  
[backtoschool.drugabuse.gov](http://backtoschool.drugabuse.gov)  
[clubdrugs.gov](http://clubdrugs.gov)  
[teens.drugabuse.gov](http://teens.drugabuse.gov)

### For Physician Information



[www.drugabuse.gov/nidamed](http://www.drugabuse.gov/nidamed)

### Other Web Sites

Information on prescription drug abuse is also available through the following Web site:

- Substance Abuse and Mental Health Services Administration Health Information Network:  
[www.samhsa.gov/shin](http://www.samhsa.gov/shin)

## U.S. Department of Health and Human Services

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## Part B: 20 Questions and Answers Regarding Methadone Maintenance Treatment Research

### Question 1: Is methadone maintenance treatment effective for opioid addiction?

**Answer:** Yes. Research has demonstrated that methadone maintenance treatment is an effective treatment for heroin and prescription narcotic addiction when measured by

- Reduction in the use of illicit drugs
- Reduction in criminal activity
- Reduction in needle sharing
- Reduction in HIV infection rates and transmission
- Cost-effectiveness
- Reduction in commercial sex work
- Reduction in the number of reports of multiple sex partners
- Improvements in social health and productivity
- Improvements in health conditions
- Retention in addiction treatment
- Reduction in suicide
- Reduction in lethal overdose

### Research Highlights

- Recent meta-analyses have supported the efficacy of methadone for the treatment of opioid dependence. These studies have demonstrated across countries and populations that methadone can be effective in improving treatment retention, criminal activity, and heroin use (Mattick, Breen, Kimber, et al., 2003; Marsch, 1998).
- An overview of 5 meta-analyses and systematic reviews, summarizing results from 52 studies and 12,075 opioid-dependent participants, found that when methadone maintenance treatment was compared with methadone detoxification treatment, no treatment, different dosages of methadone, buprenorphine maintenance treatment, heroin maintenance treatment, and L-a-acetylmethadol (LAAM) maintenance treatment, methadone maintenance treatment was more effective than detoxification, no treatment, buprenorphine, LAAM, and heroin plus methadone. High doses of methadone are more effective than medium and low doses (Amato, Davoli, Perucci, et al., 2005).
- Patients receiving methadone maintenance treatment exhibit reductions in illicit opioid use that are directly related to methadone dose, the amount of psychosocial counseling, and the period of time that patients stay in treatment. Patients receiving methadone doses of 80 to 100 mg have improved treatment retention and decreased illicit drug use compared with patients receiving 50 mg of methadone (Strain, Bigelow, Liebson, et al., 1999). Patients staying in treatment for longer periods of time showed greater improvements than those who stayed in treatment for shorter periods (Sells and Simpson, 1976; Simpson, 1993).
- A systematic review conducted on 28 studies involving 7,900 patients has demonstrated significant reductions in HIV risk behaviors in patients receiving methadone maintenance (Gowing, Farrell, Bornemann, et al., 2004). In one study that followed two separate cohorts of HIV-negative injection opioid users, HIV seroconversion occurred in 22 percent of 103 out-of-

treatment subjects compared with 3.5 percent of 152 subjects receiving methadone (Metzger, Woody, McLellan, et al., 1993).

- A randomized clinical trial in Bangkok, Thailand, included 240 heroin-dependent patients, all of whom had previously undergone at least 6 detoxification episodes. The patients were randomly assigned to methadone maintenance versus 45-day methadone detoxification. The study found that the methadone maintenance patients were more likely to complete 45 days of treatment, less likely to have used heroin during treatment, and less likely to have used heroin on the 45th day of treatment (Vanichseni, Wongsuwan, Choopanya, et al., 1991).
- In the Treatment Outcome Prospective Study (TOPS), methadone maintenance patients who remained in treatment for at least 3 months experienced dramatic improvements during treatment with regard to daily illicit opioid use, cocaine use, and predatory crime. These improvements persisted for 3 to 5 years following treatment, but at reduced levels (Hubbard, Marsden, Rachal, et al., 1989).
- In a study of 933 heroin-dependent patients in methadone maintenance treatment programs, during episodes of methadone maintenance, there were (1) decreases in narcotic use, arrests, criminality, and drug dealing; (2) increases in employment and marriage; and (3) diminished improvements in areas such as narcotic use, arrest, criminality, drug dealing, and employment for patients who relapsed (Powers and Anglin, 1993).
- In a 2.5-year followup study of 150 opioid-dependent patients, participation in methadone maintenance treatment resulted in a substantial improvement along several relatively independent dimensions, including medical, social, psychological, legal, and employment problems (Kosten, Rounsaville, and Kleber, 1987).
- A study that compared ongoing methadone maintenance with 6 months of methadone maintenance followed by detoxification demonstrated that methadone maintenance resulted in greater treatment retention (median, 438.5 vs. 174.0 days) and lower heroin use rates than did detoxification. Methadone maintenance therapy resulted in a lower rate of drug-related (mean [SD] at 12 months, 2.17 [3.88] vs. 3.73 [6.86]) but not sex-related HIV risk behaviors and a lower score in legal status (mean [SD] at 12 months, 0.05 [0.13] vs. 0.13 [0.19]) (Sees, Delucchi, Masson, et al., 2000).

**Patient Status Before and After Methadone Maintenance Treatment**—A study by McGlothlin and Anglin (1981) examined patients from three methadone maintenance treatment programs.

Figures 1 through 5 provide the results from all three programs, which illustrate that methadone maintenance treatment is effective in improving patients' lives in terms of time spent (1) using narcotics daily, (2) unemployed, (3) involved in crime, (4) dealing drugs, and (5) incarcerated.

The left side of each graph describes patient behavior before methadone maintenance treatment, and the right side of each graph depicts patient behavior following methadone maintenance treatment, including the behavior of patients who left treatment before the year ended.

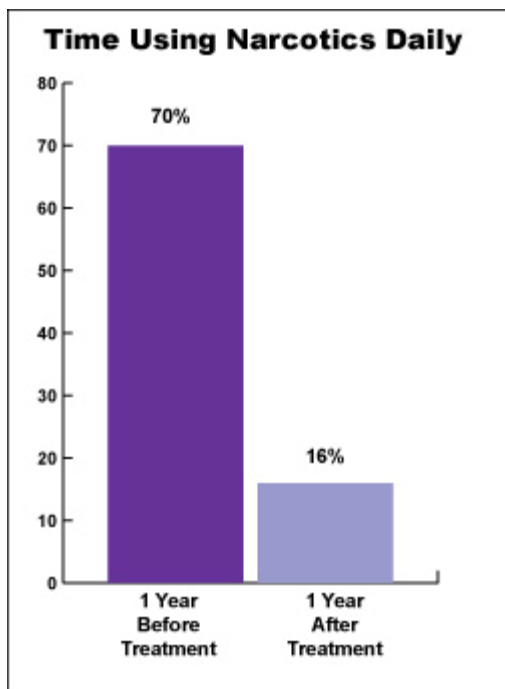


Figure 1 illustrates that the percentage of time using daily narcotics was much greater before methadone maintenance treatment than after (McGlothlin and Anglin, 1981).

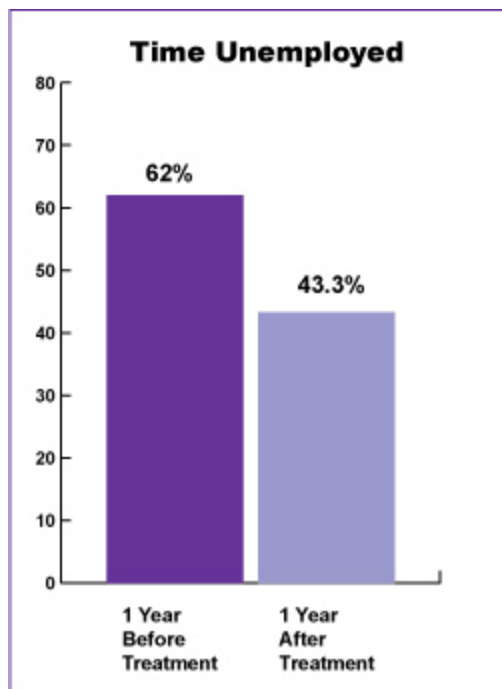


Figure 2 illustrates that the percentage of time unemployed decreased after methadone maintenance treatment (McGlothlin and Anglin, 1981).

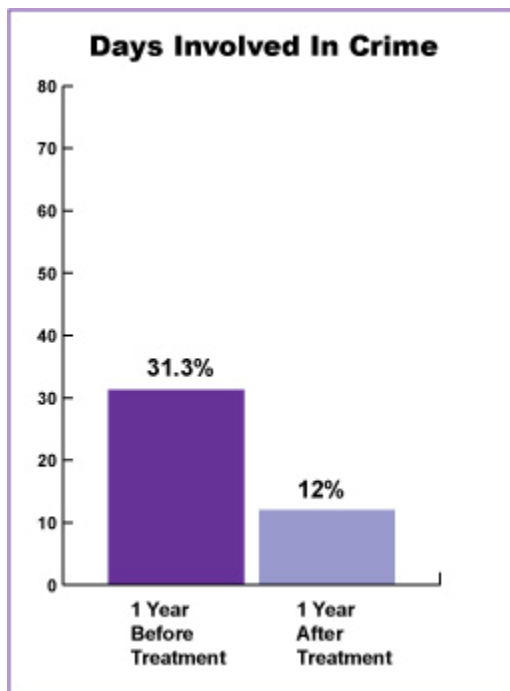


Figure 3 illustrates that the percentage of days the patient was involved in crime decreased after methadone maintenance treatment (McGlothlin and Anglin, 1981).

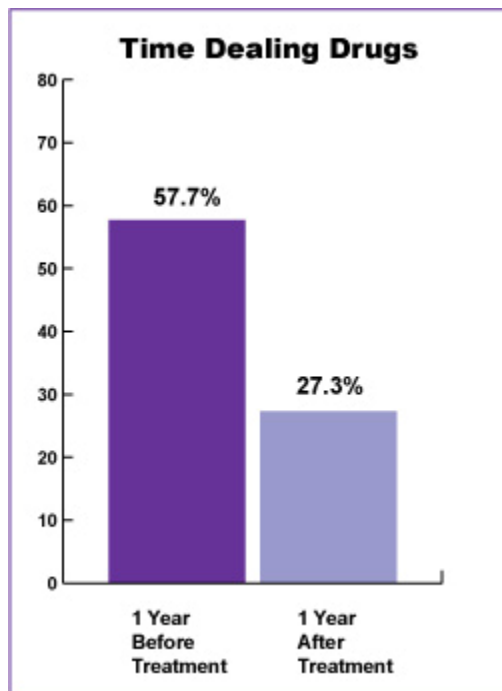
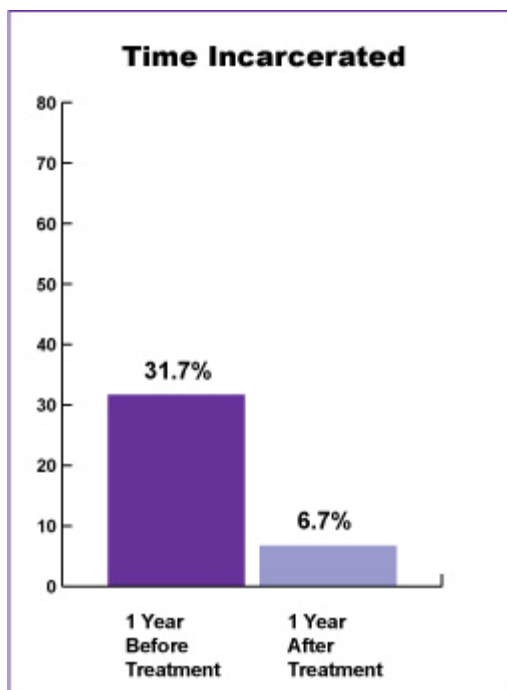


Figure 4 illustrates that the percentage of time dealing drugs decreased after methadone maintenance treatment (McGlothlin and Anglin, 1981).





**Figure 5 illustrates that the percentage of time incarcerated decreased after methadone maintenance treatment (McGlothlin and Anglin, 1981).**

### The Effects of Opioids (Heroin or Prescription Narcotics) and Methadone on Functional State—

Figures 6 and 7 illustrate how opioids and methadone have different effects on a patient's functional states and moods: repeated use of heroin or prescription narcotics causes multiple cycles of elevation and depression, but methadone promotes a relatively steady state.

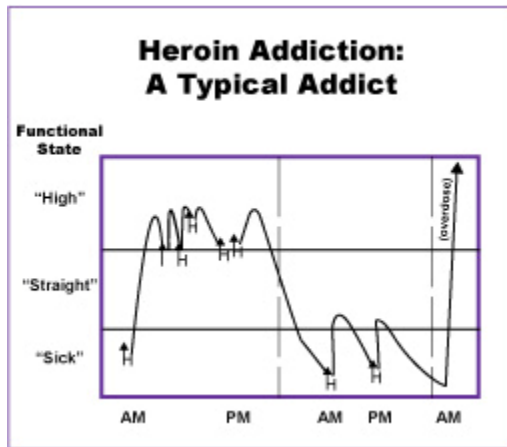
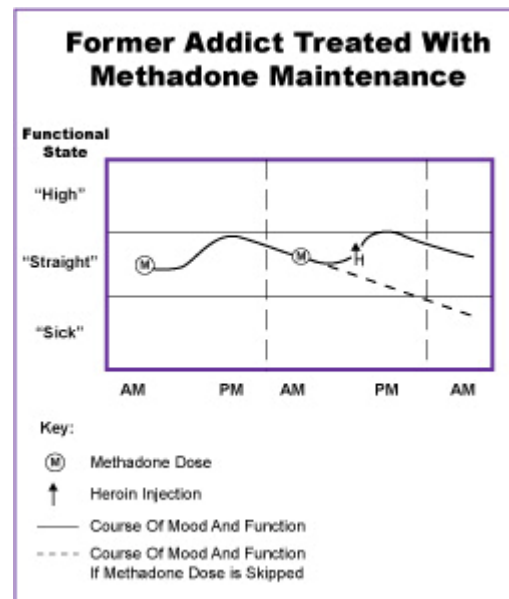
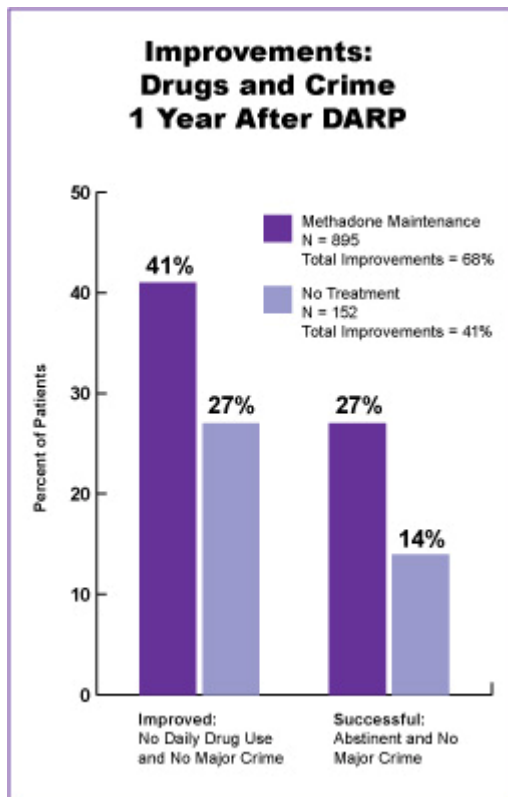


Figure 6 illustrates a typical day for a person who is opioid dependent. Note that the opioid-dependent person generally uses opioids several times each day. Each use causes an elevation in mood: the user feels "high." This high is followed by a rapid decline in mood and functional state: the user no longer feels high and may begin to feel sick. At the end of the day, or in the morning, the user feels quite sick as the result of opioid withdrawal. Overall, a typical day includes several cycles of elevated and depressed mood and functional state. As an opioid-dependent person uses opioids for a period of time (e.g., weeks to months), that person's level of physical dependence makes it less likely that he or she will experience the high. Continued drug use results from a desire to avoid the depressions and physical symptoms associated with opioid withdrawal.



In contrast, Figure 7 illustrates that a single oral dose of methadone in the morning promotes a relatively steady state of mood and function. This graph also demonstrates that use of an opioid (e.g., injection of heroin) during methadone maintenance treatment has a less intense effect on mood and function than an injection of heroin in active users who are not in methadone treatment. The dotted line in Figure 7 predicts the course of a patient's mood and function if a dose of methadone is omitted. Dole, Nyswander, and Kreek (1966) found that the decline in mood and function is gradual, not steep.

**Improvements: Drugs and Crime 1 Year After the Drug Abuse Reporting Program Study (DARP)**—The DARP study (Simpson and Sells, 1982) demonstrates that methadone maintenance treatment is effective in reducing two problems associated with heroin addiction: illicit drug use and crime. The study compared reductions in illicit drug use and crime by patients who received methadone maintenance treatment and by patients who received no treatment.



**Figure 8 illustrates that, during the first year after treatment, 41 percent of methadone maintenance treatment patients were no longer addicted to illicit opioids and were not involved in major crime. In contrast, 27 percent who received no treatment were no longer addicted to illicit opioids and were not involved in major crime (Simpson and Sells, 1982).**

Twenty-seven percent of methadone maintenance treatment patients had not used any illicit drugs and had no arrests or incarcerations during the year after methadone maintenance treatment. In contrast, 14 percent of those not treated reported no illicit drug use or arrests. Overall, 68 percent of methadone maintenance treatment patients experienced significant improvements regarding illicit drug use and crime in contrast to roughly 41 percent of those not treated.

**The Effect of Methadone Maintenance Treatment Duration on Drug Use and Crime**—The DARP study also shows that the longer patients stay in treatment, the more likely they are to remain crime free.

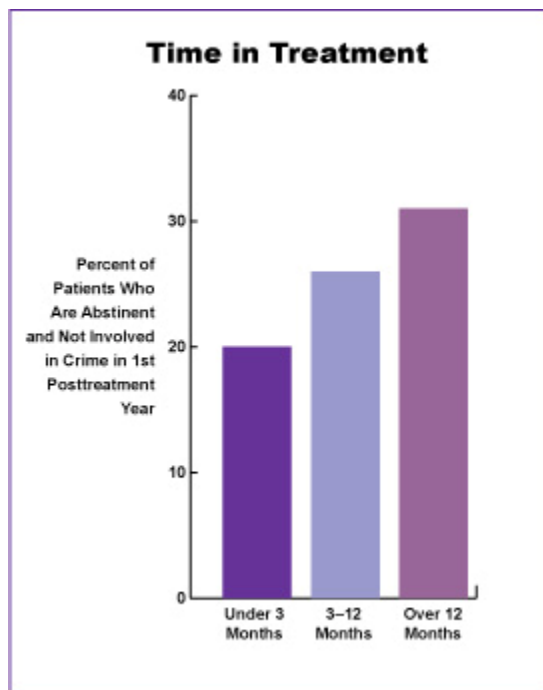


Figure 9 illustrates that there is a relationship between how long patients remain in treatment and how well they function after treatment. In this instance, the length of treatment was associated with abstinence from illicit drug use and an absence of crime. Thirty percent of patients who stayed in treatment for more than 12 months abstained from illicit drug use and criminal activity. Twenty-five percent of patients in treatment from 3 to 12 months stopped using illicit drugs and committing crimes; of those who were in treatment for under 3 months, 20 percent abstained (Simpson and Sells, 1982).

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## Question 2: Does methadone maintenance treatment reduce illicit opioid use?

**Answer:** Yes. Patients' illicit opioid use declines, often dramatically, during methadone maintenance treatment. However, adequate methadone dosage and basic psychosocial services are essential for treatment effectiveness.

### Research Highlights

Condelli and Dunteman (1993) examined a sample of 526 patients admitted to 17 methadone maintenance treatment programs that participated in the Treatment Outcome Perspective Study (TOPS). This analysis compared the length of methadone maintenance treatment with heroin use. The average short-term treatment duration was 31 days; long-term, 233 days; and continuous, 725 days. The rate of heroin use was 100 percent before treatment, 39 percent after short-term treatment, 40 percent after long-term treatment, and 17 percent after continuous treatment. This study suggests that longer exposure to methadone maintenance treatment decreases the likelihood of heroin use.

A study of 933 heroin addicts participating in methadone maintenance treatment programs compared behavior during periods on and off methadone maintenance. The study demonstrated that during periods on methadone maintenance, illicit narcotic use decreased significantly and reduction in illicit narcotic use was the most prominent effect among nine indicators of treatment success (Powers and Anglin, 1993).

In the Drug Abuse Reporting Program (DARP) study, 44 percent of the 895 patients who entered methadone maintenance treatment reported no daily use of illicit narcotics in the first posttreatment year. This represented a 56-percent decrease from 100-percent daily use in the 2 months before admission (Simpson and Sells, 1982).

### Methadone Dose

In the Ball and Ross studies (1991), patients reduced their use of injected heroin by 71 percent compared with preadmission levels. Illicit opioid use was directly related to methadone dosage: in patients on doses above 71 mg per day, no heroin use was detected, whereas patients on doses below 46 mg per day were 5.16 times more likely to use heroin than those receiving higher doses.

The impact of methadone dose has been demonstrated consistently across studies and countries. Higher (e.g., greater than 50 mg) doses of methadone are associated with better treatment retention and decreased illicit drug use (Strain, Stitzer, Liebson, et al., 1993; Strain, Bigelow, Liebson, et al., 1999; Capplehorn and Bell, 1991; Capplehorn, Bell, Kleinbaum, et al., 1993; Faggiano, Vigna-Taglianti, Versino, et al., 2003).

A meta-analysis (Faggiano et al., 2003) of 21 studies concluded that methadone dosages ranging from 60 to 100 mg per day were more effective than lower dosages in retaining patients and in reducing use of heroin and cocaine during treatment.

The following outcomes in the meta-analysis were noted:

**Retention rate**—randomized clinical trials: high versus low doses at short duration followup: RR = 1.36 [1.13 to 1.63], and at longer duration followup: RR = 1.62 [0.95 to 2.77]

**Self-reported opioid use**—randomized clinical trials: high versus low doses WMD = -2.00 [4.77 to 0.77], high versus medium doses WMD = -1.89 [-3.43 to -0.35]

**Opioid abstinence by urine toxicology at greater than 3 to 4 weeks**—randomized clinical trials: high versus low doses RR = 1.59 [1.16 to 2.18], high versus medium doses RR = 1.51 [0.63 to 3.61]

**Cocaine abstinence by urine toxicology at greater than 3 to 4 weeks**—randomized clinical trials: high versus low doses RR = 1.81 [1.15 to 2.85]

**Overdose mortality**—high dose versus low dose at 6 years' followup: RR = 0.29 [0.02 to 5.34]; high dose versus medium dose at 6 years' followup: RR = 0.38 [0.02 to 9.34]; medium dose versus low dose at 6 years' followup: RR = 0.57 [0.06 to 5.06]

One study noted lower rates of opioid-positive urine samples (53% vs. 62%,  $p < .05$ ) in patients who were being treated with 80 to 100 mg of methadone compared with those who were being treated with 40 to 50 mg (Strain et al., 1999).

### **Counseling Services**

Counseling services improve treatment outcomes over the provision of methadone alone (Amato, Minozzi, Davoli, et al., 2004). The importance of adding counseling services to methadone maintenance was demonstrated in a study that randomly assigned new patients to three levels of care: (1) methadone alone, (2) methadone plus standard counseling services, and (3) methadone plus enhanced services (counseling, medical/psychiatric, employment, and family therapy services). Patients who received the standard or enhanced services had higher treatment retention rates and less opiate use than those who received methadone alone (McLellan, Arndt, Metzger, et al., 1993). A cost-effectiveness analysis of these subjects after 1 year revealed that the standard counseling services were most cost-effective (Kraft, Rothbard, Hadley, et al., 1997).

### **Treatment Duration**

In one study, 82 percent of 105 patients who discontinued methadone relapsed to intravenous drug use within 12 months (Ball and Ross, 1991). Concerns over high relapse rates have led authorities to advocate for maintenance treatment as long as the patient (1) continues to benefit, (2) wishes to remain, (3) is at risk of relapse, (4) suffers no significant side effects, and (5) stays in treatment as long as treatment is needed, as determined by the clinician (Payte and Khuri, 1993).

DARP studies of opioid-dependent patients 12 years following admission to treatment showed that illicit opioid use declined progressively over time until year 6, when it stabilized at about 40 percent for “any” use and 25 percent for “daily” use (Simpson, Joe, Lehman, et al., 1986).

In both the DARP and TOPS studies, long treatment duration was the strongest predictor of reduced heroin use among methadone maintenance patients.

**Reductions in Illicit Opioid Use During and After Methadone Maintenance Treatment**—The DARP and TOPS studies of two different groups of heroin-addicted patients were conducted several years apart. Both demonstrated about a 40-percent reduction in illicit opioid use at the end of 1 year after methadone maintenance treatment.

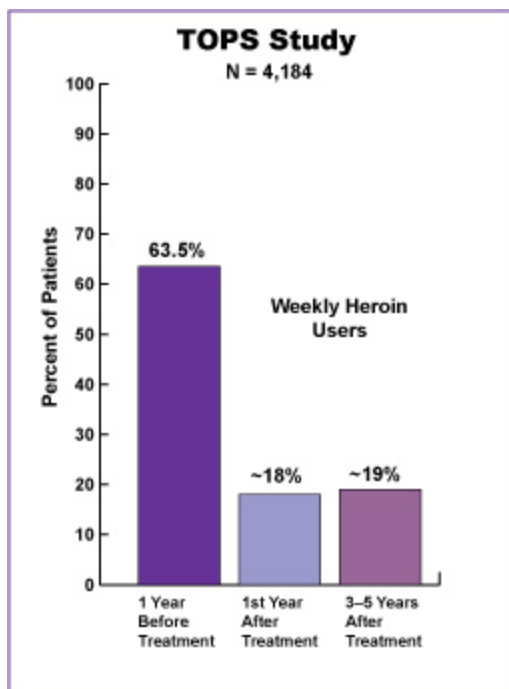


Figure 10 illustrates that, in the TOPS study, almost 64 percent of the patients used heroin at least weekly in the year before treatment; however, about 18 percent used heroin at least weekly in the year after treatment, and about 19 percent continued heroin use weekly 3 to 5 years after treatment (Hubbard, Marsden, Rachal, et al., 1989).

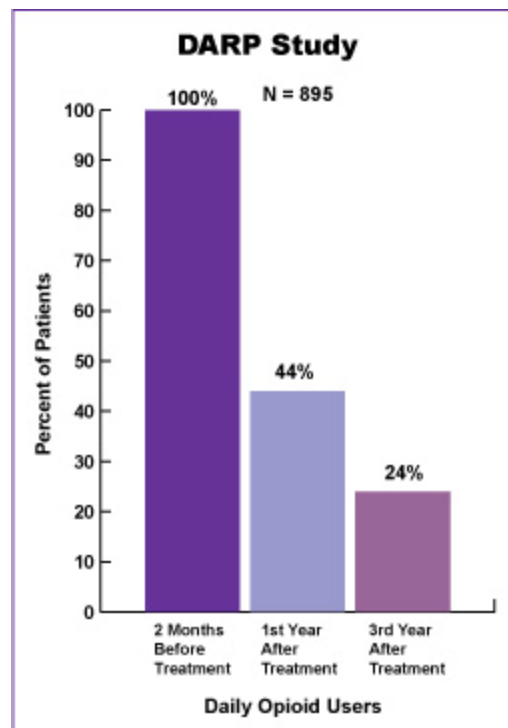
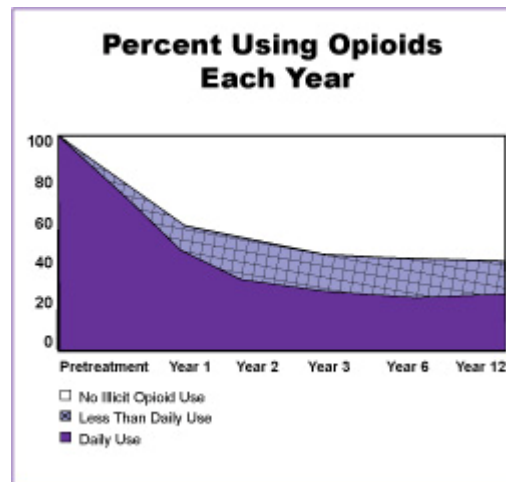


Figure 11 illustrates that in the DARP study, 44 percent of methadone maintenance treatment patients used heroin daily in the year following treatment and 24 percent used heroin daily 3 years after treatment. This represents significant reductions from the 100 percent who had used heroin daily in the 2 months before admission (Simpson and Sells, 1982). Daily illicit opioid use continued to decline steadily for the next 3 years.

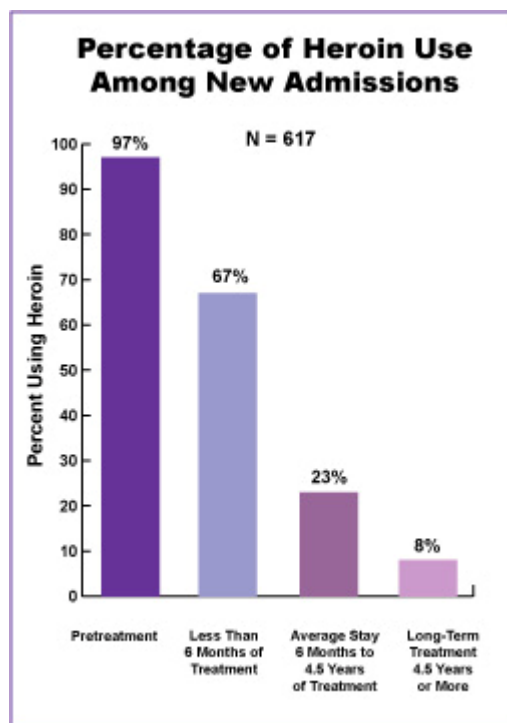


**DARP: Changes in Illicit Opioid Use: Pretreatment to 12-Year Followup**—Among patients in the DARP studies, (1) methadone maintenance treatment resulted in a rapid decline in illicit opioid use and (2) this reduction in illicit opioid use remained steady for 12 years (Simpson and Sells, 1990).



**Figure 12 illustrates that improvements among patients who used no illicit opioids and who used opioids less than daily persisted into the 12th year after treatment. About one-half of those patients treated with methadone maintenance reported no illicit drug use after 12 years. The benefits associated with methadone maintenance treatment seem to improve over time. For example, at the end of 1 year, about 50 percent of the subjects reported daily illicit drug use, but by year 12, the proportion using illicit drugs on a daily basis was reduced to about 25 percent (Simpson and Sells, 1990).**

**Reduction of Heroin Use by Length of Stay in Methadone Maintenance Treatment**—The length of stay in methadone maintenance treatment is associated with a reduction in heroin use: longer lengths of stay are associated with greater reductions in heroin use. In addition, leaving methadone maintenance treatment is associated with a return to injection drug use in 82 percent of patients within 1 year (Ball and Ross, 1991).



**Figure 13 illustrates that heroin use among a group of 617 new admissions was nearly 100 percent. Among patients who stayed in treatment for less than 6 months, about 67 percent reported using heroin. Among patients whose average stay in methadone maintenance treatment was 6 months to 4.5 years, about 23 percent reported using heroin. Among patients who remained in treatment more than 4.5 years, about 8 percent reported using heroin (Ball and Ross, 1991).**

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### **Question 3: Does methadone maintenance treatment reduce HIV risk behaviors and the incidence of HIV infection among opioid-dependent injection drug users?**

**Answer:** Yes. The daily oral administration of adequate dosages of methadone reduces the need for opioid-dependent individuals to inject drugs. By decreasing injection drug use, methadone maintenance treatment helps reduce the spread of diseases transmitted through needle sharing, such as human immunodeficiency virus (HIV) infection, hepatitis C virus (HCV), and other bloodborne infections (Sullivan, Metzger, Fudala, et al., 2005; Gowing, Farrell, Bornemann, et al., in press).

#### **Research Highlights**

A systematic review of 23 studies of 7,900 patients in diverse countries and settings reported significant decreases in the following HIV risk behaviors among patients receiving methadone maintenance treatment: (1) the proportion of opioid-dependent injection drugs, (2) the reported frequency of injection, (3) levels of sharing of injection equipment, (4) illicit opioid use, (5) reduction in the proportion of opioid-dependent injection drug users reporting multiple sex partners or exchanges of sex for drugs or money, and (6) reductions in cases of HIV infection among opioid-dependent injection drug users. However, it should be noted that methadone treatment had little or no effect on the use of condoms. The authors concluded that the provision of agonist treatment for opioid dependence should be supported in countries with emerging HIV and injection drug use problems as well as in countries with established populations of injection drug users (Gowing, Farrell, Bornemann, et al., 2004).

These results support an earlier meta-analysis of 11 studies that found a consistent, statistically significant relationship between methadone maintenance treatment and the reduction of HIV risk behaviors. This meta-analysis found that methadone maintenance treatment had a small-to-moderate effect in reducing HIV risk behaviors (Marsch, 1998).

- A study that evaluated HIV risk behavior in patients receiving ongoing methadone maintenance compared with patients receiving 6 months of methadone maintenance followed by detoxification demonstrated that those patients who received ongoing methadone maintenance treatment reported lower HIV drug (but not sex) risk behaviors after 6 and 12 months of treatment (Sees, Delucchi, Masson, et al., 2000).
- In New Haven, CT, 107 methadone-maintained injection drug users who were not in treatment were surveyed regarding their risk behaviors. The frequency of injections was found to be 50 to 65 percent ( $p < .001$ ) higher among the out-of-treatment subjects (Meandzija, O'Connor, Fitzgerald, et al., 1994).
- In a 3-year field study of methadone maintenance treatment programs in New York, NY, Philadelphia, PA, and Baltimore, MD, treatment was found to be effective in reducing injection drug use and needle sharing by most heroin addicts. Of 388 patients who remained in treatment for 1 year or more, 71 percent had stopped injection drug use. Conversely, 82 percent of patients who left treatment relapsed rapidly to injection drug use (Ball, Lang, Meyers, et al., 1988).
- Abdul-Quader, Friedman, Des Jarlais, et al. (1987) reported that both the frequency of drug injection and the frequency of drug injection in shooting galleries were significantly reduced by the amount of time spent in methadone maintenance treatment.
- A study by Serpelloni, Carrieri, Rezza, et al. (1994) examined the effect of methadone maintenance treatment on HIV infection incidence among injection drug users. The study found that the amount of time spent in methadone maintenance treatment was the major determinant in remaining HIV-free, which confirms the effectiveness of long-term programs in reducing the risk of HIV infection. Indeed, the risk of HIV infection increased 1.5 times for every 3 months spent out of methadone treatment in the past 12 months immediately preceding seroconversion. The study noted that higher daily methadone doses were associated with a reduction in HIV infection.



- A study by Weber, Ledergerber, Opravil, et al. (1990) examined the role of methadone maintenance treatment in reducing the progression of HIV infection among 297 current and former injection drug users with asymptomatic HIV infection. The study showed that HIV infection progresses significantly more slowly in those who receive methadone maintenance treatment and those who are drug free than in active injection drug users.
- In Philadelphia, PA, a longitudinal study of HIV infection and risk behaviors among 152 injection drug users in methadone maintenance treatment and 103 out-of-treatment injection drug users found significantly lower rates of risk behavior, including needle sharing, injection frequency, shooting gallery use, and visits to crack houses among the methadone-maintained users. While 70 percent of the out-of-treatment cohort reported sharing needles during the 6 months before entry into the study, only 30 percent of those in treatment reported sharing needles during this same interval.
- At entry into this study, 18 percent of the out-of-treatment subjects and 11 percent of the methadone-maintained clients tested positive for antibodies to HIV. After 18 months of study, 33 percent of the out-of-treatment cohort were infected, whereas 15 percent of the methadone clients tested positive ( $p < 0.01$ ). The incidence of new infection was strongly associated with the level of participation in methadone treatment. Among those who remained in methadone treatment for the entire 18-month study period, 3.5 percent became infected. Among those who remained out of treatment, 22 percent became infected with HIV (Metzger, Woody, McLellan, et al., 1993).
- Another study of HIV seroconversion followed 56 patients who were continuously enrolled in methadone maintenance and compared them with 42 patients who had intermittent methadone treatment. Subjects in continuous treatment had a seroconversion rate of 0.7 per 100 person years (95% CI = 0.1, 5.3), and those with interrupted treatment had a rate of 4.3 per 100 person years (95% CI = 2.2, 8.6) (Williams, McNelly, Williams, et al., 1992).
- A relatively short-term study of methadone maintenance versus control in a prison system in Australia found reductions in opioid use but no changes in HIV or HCV incidence (Dolan, Shearer, MacDonald, 2003).

The following two visuals—HIV Infection Rates by Methadone Maintenance Treatment Status and 18-Month HIV Seroconversion by Methadone Maintenance Treatment Retention—depict findings from this study.

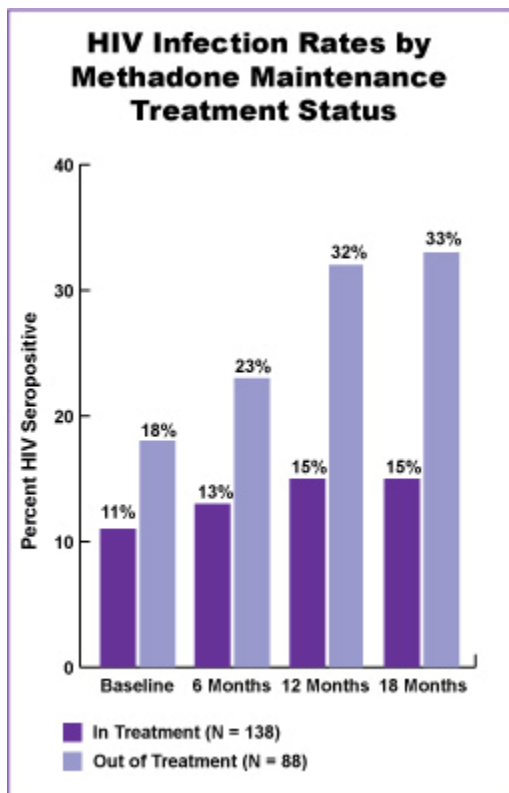


Figure 14 illustrates that at the beginning of this study, 18 percent of the out-of-treatment subjects and 11 percent of the methadone-maintained clients tested positive for antibodies to HIV. After 18 months, nearly twice as many (33 percent) of the out-of-treatment cohort were HIV-positive, whereas only 15 percent of the methadone clients tested positive ( $p < .01$ ). The incidence of new infection was strongly associated with the level of participation in methadone treatment.

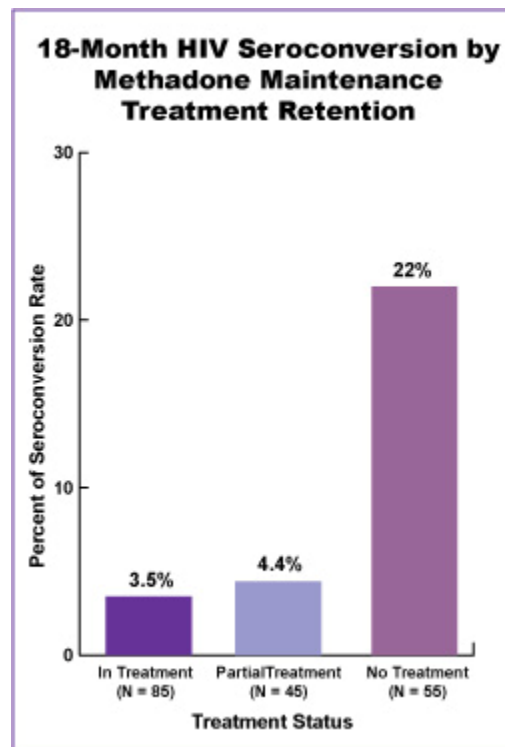
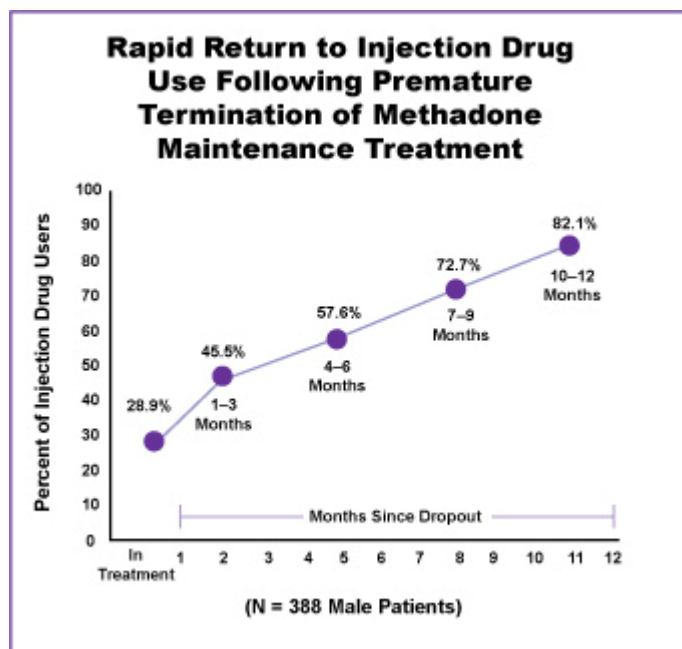


Figure 15 illustrates that among those who remained in methadone maintenance treatment for the entire 18-month study period, 3.5 percent became infected with HIV. Among those who remained out of treatment, 22 percent became infected with HIV (Metzger et al., 1993).

**Rapid Return to Injection Drug Use Following Premature Termination of Methadone Maintenance Treatment**—In a 3-year field study of methadone maintenance treatment programs in New York, NY, Philadelphia, PA, and Baltimore, MD, methadone maintenance treatment was found to be effective in reducing injection drug use and needle sharing by most heroin addicts. Of 388 patients who remained in treatment for 1 year or more, 71 percent had stopped injection drug use. Conversely, 82 percent of the 105 patients who left treatment relapsed rapidly to injection drug use (Ball et al., 1988).



**Figure 16 illustrates that methadone maintenance treatment is associated with reductions in injection drug use and the risks related to HIV infection. When drug users leave methadone maintenance treatment prematurely, they have an increased likelihood of returning to injection drug use (Ball et al., 1988).**

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#### **Question 4: Does methadone maintenance treatment reduce criminal activity?**

**Answer:** Yes. Patients are less likely to become involved in criminal activity while in methadone maintenance treatment.

- Patients who remain in methadone maintenance treatment for long periods of time are less likely to be involved in criminal activity than patients in treatment for short periods.
- The availability of methadone maintenance treatment in a community is associated with a decrease in that community's criminal activity, particularly theft.

#### **Research Highlights**

- In a meta-analysis of 24 studies, results indicate an overall small-to-medium effect of  $r = -0.25$  (unweighted) of the impact of methadone maintenance on criminal activity. A large effect size of  $r = 0.70$  (unweighted) was seen in those studies that investigated the efficacy of methadone maintenance treatment in reducing drug-related criminal behaviors. A small-to-moderate effect of  $r = 0.23$  (unweighted) was obtained when both drug and property-related criminal activities were evaluated. Finally, a small effect of  $r = 0.17$  (unweighted) was demonstrated when drug- and nondrug-related criminal behaviors were combined (Marsch, 1998).
- In the Treatment Outcome Perspective Study (TOPS), 32 percent of the methadone maintenance patients acknowledged committing one or more predatory crimes in the year before treatment, but only 10 percent continued these activities during treatment. By 3 to 5 years after leaving treatment, only 16 percent of the patients reported predatory criminal activity—a reduction of one-half the pretreatment level (Hubbard, Marsden, Rachal, et al., 1989).
- Among the 617 patients studied by Ball and Ross (1991), there was a 70.8-percent decline in crime-days within the 4-month methadone maintenance treatment period. This decline was followed by continuing, but less dramatic, declines in mean crime-days among those in treatment for 1 to 3 years. Those in treatment for 6 or more years had the lowest rate of crime-days per year (14.5).
- The Powers and Anglin (1993) retrospective study of 933 heroin addicts demonstrated that rates of criminality, arrests, and drug dealing decreased during episodes of methadone maintenance treatment when compared with addicts not in treatment.
- In the National Treatment Outcome Research Study, acquisitive criminal behavior decreased in the majority of the 333 patients except those ( $n = 88$ ) who were felt to have a poor treatment response. In these patients, there was no change in this type of criminal activity (Gossop, Marsden, Stewart, et al., 2000).
- The meta-analysis by Mattick, Breen, Kimber, et al. (2003) revealed that criminal activity declined in consort with reductions in heroin use, although the advantage for methadone beyond control in reducing criminal activity was not statistically significant (3 studies, 363 patients:  $RR = 0.39$ , 95% CI: 0.12-1.25).

**The Effects of Methadone Maintenance Treatment on Crime-Days**—The Ball and Ross study (1991) of 617 patients demonstrated that methadone maintenance treatment is associated with a dramatic decline in the average number of crime-days per year.

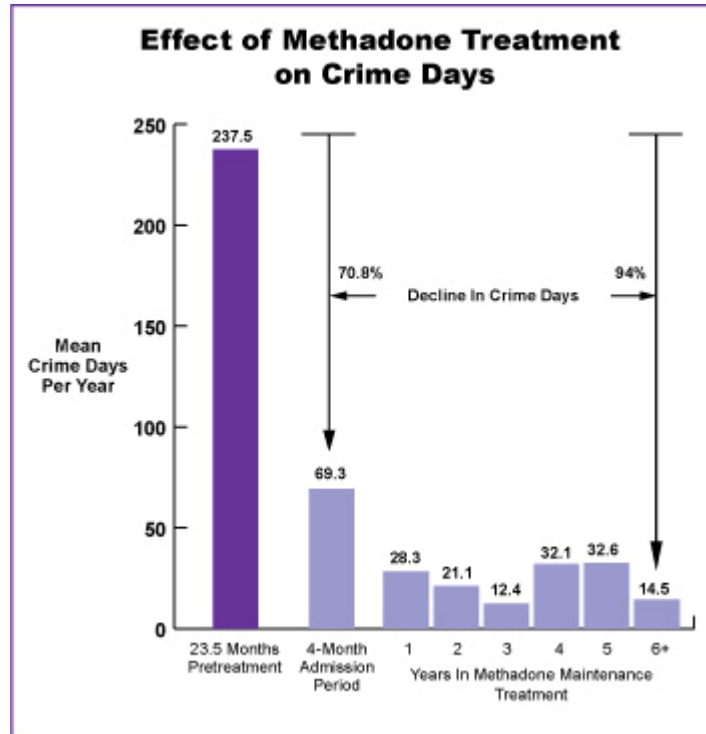


Figure 17 illustrates that the average number of crime-days per year before treatment was 237. During the 4-month initial methadone maintenance treatment, the average number of crime-days per year was 69. This represents about a 71-percent decline. This dramatic decline was followed by continuing, but less dramatic, declines in the average number of crime-days among those in methadone maintenance treatment for 1 to 3 years. Patients who remained in methadone maintenance treatment for 6 or more years reported only 14.5 crime-days per year, representing a 94-percent decline in average number of crime-days (Ball and Ross, 1991).

**Crime Before and During Methadone Maintenance Treatment at Six Programs**—Ball and Ross (1991) found a dramatic decline in crime when comparing pretreatment crime-days per year and the number of crime-days per year after 6 months or more in methadone maintenance treatment.

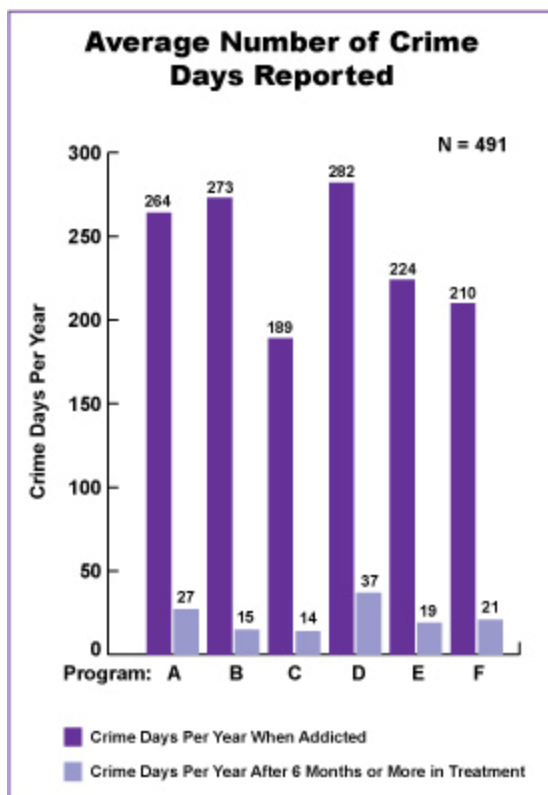


Figure 18 illustrates the average number of crime-days reported by patients in six methadone maintenance treatment programs. Although there are differences among programs, the dramatic decrease in crime-days before and during methadone maintenance treatment occurs for all six programs. Crime was reduced by approximately 90 percent in program A, 95 percent in program B, 93 percent in program C, 87 percent in program D, 92 percent in program E, and 90 percent in program F. The average reduction in crime for those in methadone maintenance treatment was just over 91 percent (Ball and Ross, 1991).

The cost benefits of methadone maintenance treatment become obvious when one compares the costs of providing treatment with the social costs that would have occurred if the crime level had continued.

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### **Question 5: Does methadone maintenance treatment improve the likelihood of obtaining and retaining employment?**

**Answer:** Yes. The likelihood of becoming and remaining employed is increased for patients who participate in methadone maintenance treatment.

- In an early study of 100 chronic heroin users who were admitted to methadone maintenance treatment, the employment rate increased from 21 percent at admission to 65 percent 1 year later (Maddux and McDonald, 1973; Maddux and Desmond, 1979).
- A study of 92 males admitted to methadone maintenance treatment programs from 1971 through 1973 demonstrated that, following methadone maintenance treatment, employment increased about 18 percent (Harlow and Anglin, 1984).
- In a 10-year followup study, 95 chronic opioid users who spent at least 1 cumulative year in methadone maintenance treatment were compared with 77 chronic opioid users who spent less than 1 cumulative year in methadone maintenance treatment. Those who were on methadone maintenance treatment for more than 1 year had a higher average time employed (mean of 42 months) than those who were in treatment for less than 1 year (mean of 35 months) (Maddux and Desmond, 1992).
- The Powers and Anglin (1993) study of 933 heroin addicts in methadone maintenance treatment demonstrated that rates of employment (and marriage) increased during treatment.
- Methadone maintenance patients in the Treatment Outcome Perspective Studies (TOPS) had small changes in employment rates during and following treatment compared with pretreatment rates. Although 24 percent of the patients reported full-time employment in the year before admission, this rate did not increase significantly during treatment. It declined abruptly in the 3 months following discharge, improved to 29 percent by year 2, and dropped off again to less than pretreatment rates by years 3 to 5 following treatment (Hubbard, Marsden, Rachal, et al., 1989).
- In a study that compared ongoing methadone maintenance with 6 months of methadone maintenance followed by detoxification, no difference was seen in employment, although nearly 50 percent of patients were employed at entry into the study (Sees, Delucchi, Masson, et al., 2000). Similarly, a study comparing methadone maintenance with methadone-free treatment saw improvements in both groups over time but no difference in outcomes across treatment type (Abbot, Moore, Delaney, et al., 1999). The McLellan trial, which evaluated varying levels of ancillary services, provides some insight into these negative findings. Specifically, the group of patients in the McLellan trial that received enhanced psychosocial services (including employment counseling) was noted to have improvements in employment status with methadone treatment compared with patients who received no or standard services (McLellan, Arndt, Metzger, et al., 1993).

**Changes in Employment During and After Methadone Maintenance Treatment**—Figures 19 and 20 illustrate the effects of methadone maintenance treatment on full-time employment as demonstrated by the TOPS and DARP studies. In one study, there was little effect, but in the other, methadone maintenance treatment was associated with significant increases in full-time employment.



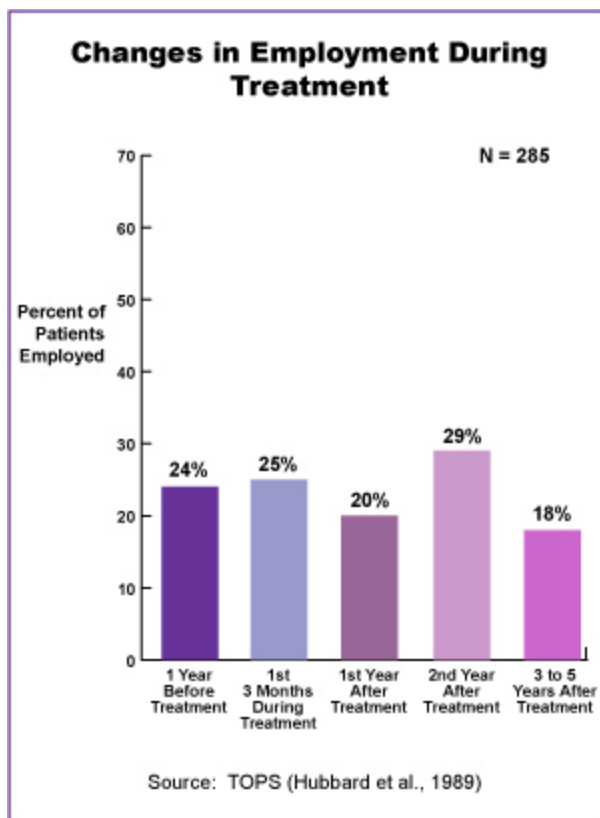
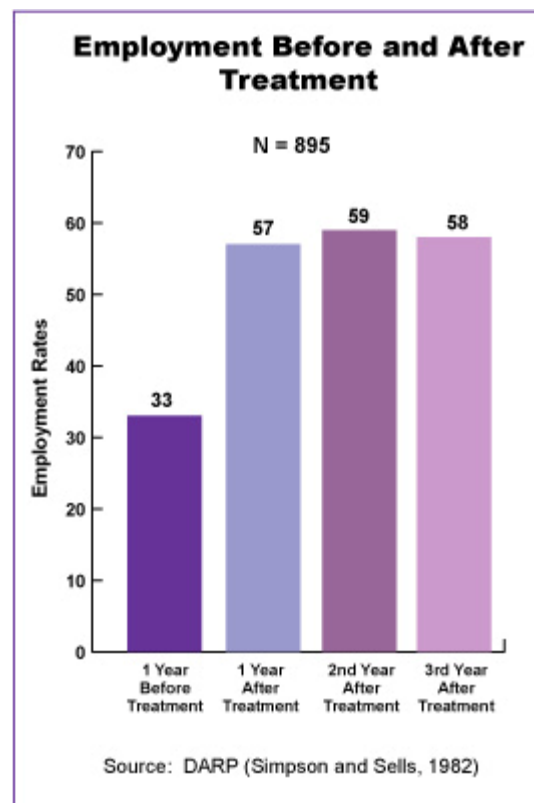


Figure 19 illustrates that patients in TOPS studies experienced small and inconsistent changes in full-time employment rates during and after treatment. Employment rates were about 24 percent 1 year before treatment, ranged from 20 to 25 percent during the first year after treatment, rose to 29 percent during the second year after treatment, and declined to 18 percent 3 to 5 years after treatment (Hubbard et al., 1989).



In contrast, Figure 20 illustrates that the DARP studies reported an abrupt increase from 33-percent full-time employment before treatment to nearly 60 percent after treatment (Simpson and Sells, 1982).

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## **Question 6: What effect can methadone maintenance treatment have on the use of alcohol and other drugs?**

**Answer:** Research outcomes are mixed regarding the effect of methadone maintenance treatment on the use of illicit drugs other than opioids. That is, some research indicates that methadone maintenance treatment is associated with decreases in the use of alcohol, cocaine, and marijuana; other research indicates increases in the use of these drugs. It is important to note that the medication methadone has no direct effect and is not intended to have an effect on rates of alcohol and other drug use. Patients receiving methadone maintenance who disengage from interactions with others who are actively using drugs are less likely to engage in these behaviors. In addition, reductions in alcohol and drug use result from the counseling services included in methadone maintenance treatment. When these services are specifically designed to reduce alcohol and other drug use, such reductions are likely.

### **Research Highlights**

- In the Drug Abuse Reporting Program (DARP) studies, there were reductions in nonopioid drug use (except marijuana) among 895 methadone maintenance patients, comparing the 2-month period before admission and the year following discharge. The reduction in nonopioid use was 13 percent—from 54 percent of patients who reported any use before admission to 41 percent at the 1-year followup point (Simpson and Sells, 1982).
- In the 12-year DARP followup study, “heavy drinking” was reported by 21 percent of the sample in the month before treatment; it rose to 31 percent during the first year afterward and then declined to 22 percent by year 12. One-half of the patients reported substituting alcohol for opioids after stopping daily illicit opioid use (Lehman, Barrett, and Simpson, 1990).
- In a study comparing buprenorphine maintenance with methadone maintenance for patients with opioid dependence and cocaine abuse, both treatments resulted in significant declines in opioid use but were indistinguishable in terms of their effect on comorbid cocaine use (Schottenfeld, Pakes, Oliveto, et al., 1997).

**Methadone Maintenance Treatment and General Drug Abuse**—Among three cohorts of new-admission patients in methadone maintenance treatment, Ball and Ross (1991) found that the use of all illicit drugs, except marijuana, decreased markedly in relation to time in treatment. These three cohorts had been in treatment 6 months, 4.5 years, or more than 4.5 years.

In the Treatment Outcome Perspective Study (TOPS), 90 percent of methadone maintenance treatment patients who reported drug use at intake reported a reduction in use during the first 3 months of treatment. For 80 percent, this reduction is large. In the year before treatment, less than 10 percent of methadone maintenance treatment patients were minimal drug users. During treatment, more than 50 percent of the patients were minimal drug users. During the 3 to 5 years after discharge, less than 32.5 percent were minimal drug users (Hubbard, Marsden, Rachal, et al., 1989).

In the National Treatment Outcome Research Study (NTORS), of 333 patients receiving methadone maintenance in the United Kingdom, overall declines were seen in the use of heroin, barbiturates, amphetamines, cocaine, and crack cocaine among patients receiving methadone maintenance. Alcohol use, however, did not change over time (Gossop, Marsden, Stewart, et al., 2000).

In another evaluation of 513 heroin users in methadone treatment in TOPS, a decline was observed in the use of cocaine, amphetamines, illegal methadone, tranquilizers, and marijuana, but not alcohol (Fairbank, Duntzman, and Condelli, 1993).

The Powers and Anglin study (1993) of 933 heroin addicts in methadone maintenance programs demonstrated that during episodes of methadone maintenance treatment, illicit opioid use decreased, but

alcohol and marijuana levels increased moderately. Kreek (1991) observed that by 1990, alcoholism was identified in 40 or 50 percent of new admissions to methadone maintenance treatment programs, and cocaine abuse was found in 70 to 90 percent. She also estimated that 20 to 46 percent of patients in effective methadone maintenance treatment programs continue using cocaine, and 15 to 20 percent of methadone maintenance treatment patients regularly inject cocaine.

**Methadone Maintenance Treatment and Cocaine Use**—Among the TOPS patients who remained in methadone maintenance treatment at least 3 months, 26.4 percent had used cocaine regularly the year before treatment. This rate fell to 10 percent during the first 3 months of treatment but returned to 16 percent by 3 to 5 years after discharge. Altogether, 40 percent of methadone maintenance treatment patients who regularly used cocaine before treatment and stayed in treatment for at least 3 months abstained from cocaine use in the year after treatment (Hubbard et al., 1989).

In the TOPS studies, although 70 percent of heroin abusers had frequently used cocaine the year before treatment, it was the primary drug of choice for only 2 percent of methadone maintenance treatment patients (Hubbard et al., 1989).

In the new admissions group of a six-program study (n = 345), 46.8 percent of 126 patients had used cocaine in the past 30 days. Among the average-stay group (up to 4.5 years in treatment), 27.5 percent still used cocaine; this rate dropped to 17.2 percent among the long-term group of 146 patients who had been in continuous treatment for more than 4.5 years (Ball and Ross, 1991).

A study evaluating the effect of methadone dose on treatment outcomes noted that patients receiving 50 mg of methadone, compared with those receiving 20 mg or 0 mg, had a reduced rate of opioid-positive urine samples (56.4% vs. 67.6% and 73.6%, respectively;  $p < 0.05$ ) and cocaine-positive urine samples (52.6% vs. 62.4% and 67.1%, respectively;  $p < 0.05$ ) (Strain, Stitzer, Liebson, et al., 1993).

A systematic review examined the impact of methadone dose on cocaine use and found three studies that addressed the question. Results from the one study in which cocaine use was based on self-reported use showed no significant excess of use of cocaine among subjects treated with higher doses compared with subjects treated with lower doses. Pooled results from the two studies that used urine analysis and looked at an abstinence period longer than 3 weeks showed that higher methadone doses increased the probability that patients would stay abstinent from cocaine, compared with lower doses (RR = 1.81 [1.15, 2.85]) (Faggiano, Vigna-Taglianti, Versino, et al., 2003).

**Methadone Maintenance and Marijuana Use**—Among TOPS subjects, marijuana use was common: 55 percent of methadone maintenance patients who stayed in treatment for 3 months reported regular use in the year before admission. This decreased to 47 percent during the first 3 months of treatment, continued to decline immediately posttreatment, and decreased even more to 36.4 percent in the 3- to 5-year period after discharge. However, marijuana use appeared more resistant to change than other illicit substances (Hubbard et al., 1989). It should be considered that the treatment programs likely did not clinically address marijuana or other drug use.

Ball and Ross (1991) found that marijuana continued to be used quite regularly (an average of 13 to 16 days per month) by high percentages of all patient groups in methadone maintenance treatment: 48.4 percent of the new admissions, 47.7 percent of the average-stay group, and 37.2 percent of the patients in treatment more than 4.5 years.

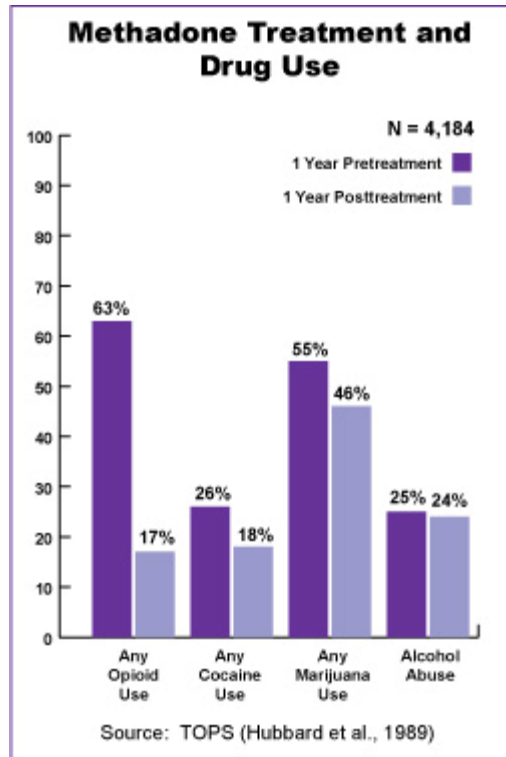
In one study of 132 opioid addicts participating in methadone maintenance treatment programs, it was noted that during episodes of methadone maintenance treatment, levels of alcohol and marijuana use increased modestly (Powers and Anglin, 1993).

**Methadone Maintenance and the Nonmedical Use of Prescription Drugs**—In the TOPS studies, the regular nonmedical use of psychoactive prescription drugs by methadone maintenance treatment patients during the first posttreatment year decreased by one-third from the pretreatment period. Although 30.3 percent of this methadone maintenance group reported regular nonmedical use of prescription drugs (i.e., barbiturates, amphetamines, tranquilizers, sedatives, and hypnotics), nonmedical prescription drug use was a primary problem for only 1.9 percent of these patients at admission (Hubbard et al., 1989).

In the NTORS study, a decline was seen in the use of benzodiazepines among patients receiving methadone maintenance (Gossop et al., 2000). In the TOPS studies, nonmedical prescription drug use declined during methadone maintenance treatment, increased immediately following discharge, and declined again to 10 percent of patients 3 to 5 years following discharge (Hubbard et al., 1989).

Ball and Ross (1991) found that although the nonmedical use of sedatives other than barbiturates was acknowledged by 31.8 percent of new admissions to methadone maintenance treatment, the percentage of sedative-using patients who had been in treatment for more than 4.5 years was less than half that of the new admission group (14.5 percent).

**Methadone Maintenance Treatment and Alcohol and Other Drug Use**—In the TOPS studies, improvements in the use of illicit and nonprescription drugs follow a pattern of (1) a dramatic reduction during treatment, (2) a sharp increase immediately after discharge, and (3) a leveling off at an impressively reduced rate for up to 5 years of followup contacts (Hubbard et al., 1989).



**Figure 21 illustrates that as reported by the TOPS study of 4,184 patients, methadone maintenance treatment was associated with reductions in (1) any illicit opioid use, (2) any cocaine use, (3) any marijuana use, and (4) alcohol abuse (the 1-percent reduction noted here is not statistically significant) (Hubbard et al., 1989).**

“Any opioid use” declined from 63 percent pretreatment to 17 percent 1 year posttreatment. This was the most dramatic decline. “Any cocaine use” declined from 26 percent to 18 percent. “Any marijuana use” declined from 55 percent pretreatment to 46 percent 1 year posttreatment. Alcohol abuse remained almost steady, declining slightly from 25 percent to 24 percent.

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## Question 7: What components of methadone maintenance treatment account for reductions in AIDS risk behaviors?

**Answer:** Reductions in drug use and related AIDS risk behaviors among methadone-maintained individuals have been associated with both physiological and psychosocial factors. Recent studies have confirmed that adequate methadone dose levels are required to achieve significant reductions in opioid abuse. At the same time, research has demonstrated that methadone alone will have, at best, limited impact. Additional psychosocial support services are needed to maximize the effectiveness of methadone maintenance treatment.

### Research Highlights

- A study examining the impact of psychosocial services in methadone treatment found that outcomes were significantly improved for those injection drug users who received services in addition to methadone (McLellan, Arndt, Metzger, et al., 1993). In this study, methadone patients were randomly assigned to one of three groups that received either: (1) methadone alone with no other services; (2) methadone and regular counseling; or (3) methadone with counseling and medical/psychiatric services, employment services, and family therapy. Although methadone doses were the same in each group, outcomes were significantly better in the groups that also received psychosocial services. Sixty-nine percent of the methadone-only group had to be “protectively transferred” due to unremitting use of opiates or cocaine or medical/psychiatric emergencies.
- Counseling programs specifically designed to reduce HIV risk behavior among methadone-maintained patients have been shown to be effective (Margolin, Avants, Warburton, et al., 2003).
- Patients with comorbid psychiatric disease are less likely to decrease their HIV risk behaviors during methadone maintenance treatment, compared with those without, although both groups receive benefit (King, Kidorf, Stoller, et al., 2000).
- A study of 291 patients that evaluated a high-intensity day treatment along with methadone versus enhanced methadone treatment saw decreases in drug use and HIV risk behavior in both groups; however, the study was unable to detect a significant difference in these outcomes between treatment groups (Avants, Margolin, Sindelar, et al., 1999).
- Similarly, a study that compared methadone dose (50 mg vs. 80 mg) and visit frequency (two visits per week vs. five visits per week) saw reductions in HIV risk behavior with methadone maintenance treatment but was unable to demonstrate a difference in HIV risk reduction between the four groups (Rhoades, Creson, Elk, et al., 1998).
- Hartel, Schoenbaum, Selwyn, et al. (1995) examined the drug use patterns and treatment characteristics of 652 methadone patients receiving treatment from the Montefiore Methadone Treatment Program in New York. The study found that those who were maintained on less than 70 mg per day of methadone were 2.1 times ( $p < .005$ ) more likely to be using heroin. It is important to note that the observed effects of higher doses were found even after controlling for the length of time in treatment.
- A meta-analysis of HIV risk reduction interventions in substance abuse treatment programs found that these programs succeeded in changing knowledge, attitudes, and beliefs; sexual behavior; and injection practices. The impact of the intervention programs was negatively correlated with the presence of ethnic/minority samples and positively correlated with the number of intervention techniques used, the intensity of the intervention, interventions that were delivered within methadone treatment, and specific intervention techniques (Prendergast, Podus, Chang, et al., 2002).

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### **Question 8: Do risk factors for HIV infection acquisition and transmission differ for women compared with men in methadone maintenance treatment?**

**Answer:** Yes. Despite nearly equal HIV infection rates for men and women in drug treatment, female injection drug users differ from males in the types and contexts of their risk behaviors. While the main HIV infection risk for both male and female injection drug users is needle sharing, women frequently support themselves and their addiction habit through sex work and are more likely to have an injection drug user as a sexual partner. The most common needle-sharing context for women is with their sex partners.

In addition, women may transmit HIV infection to their infants in utero, during delivery, or through breastfeeding. Women in methadone treatment need HIV infection prevention programs that take these gender differences into account.

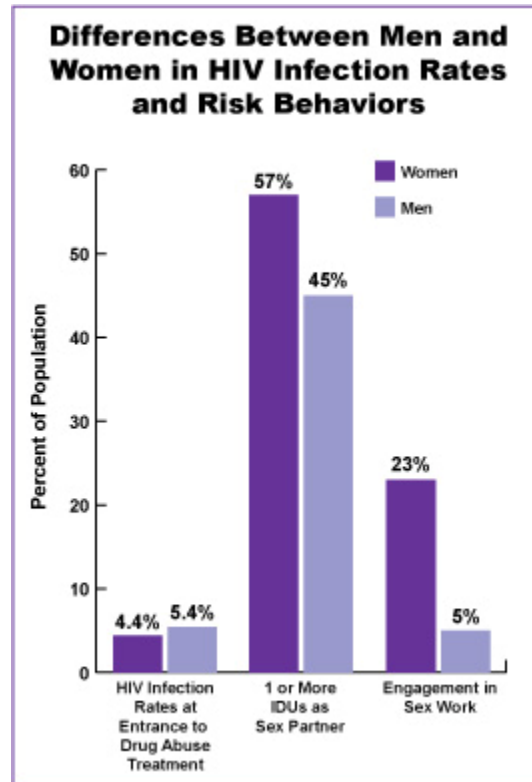
#### **Research Highlights**

- Patterns of needle sharing are different for males and females. Women tend to share needles in the context of a sexual relationship. This type of needle sharing may be more difficult to change than other types of injection risk behavior because the perception of risk or ability to negotiate safe needle use by women may be limited. In research conducted among 19,716 males and 6,609 females in the National AIDS Demonstration Research (NADR) project addressing street-recruited injection drug users, women were more likely than men to share needles with their sex partners. The majority of the participants injected only heroin or heroin in combination with cocaine (Brown and Weissman, 1994).

Research in other countries has shown a tendency for female injection drug users to share needles with their sex partners. For example, women in Glasgow, Scotland, were frequently injected with used needles and syringes from their partners (Barnard, 1993).

- Sexual risk behavior has been shown to be less likely to change among both male and female injection drug users than needle-sharing risk behavior. In addition, women who inject drugs are less likely than men to be in control of safer sex practices, such as condom use. Although methadone maintenance treatment may reduce drug use and prostitution or the exchange of sex for drugs, women may be at risk for HIV infection by their habitual sex partners. Female injection drug users tend to have drug users as sex partners, even after enrollment in treatment, and are not likely to practice safer sex with these partners. HIV risk reduction programs for women in methadone maintenance treatment must take into account the social and interpersonal context of sexual risk behavior in order to be effective (Finnegan, Davenny, and Hartel, 1993; Hartel, 1994).
- Women with HIV who are maintained on methadone may improve their access to medical care for HIV infection and disease and possibly reduce their chance of transmitting HIV to infants in utero. Both zidovudine (AZT) and nevirapine have been shown to reduce significantly the risk of mother-to-infant transmission of HIV infection (Connor, Sperling, Gelber, et al., 1994; Brocklehurst and Volmink, 2002).
- It is likely that some infants are infected during labor and delivery or after delivery through breastfeeding. Careful attention to factors that can place the infant at risk during birth and afterwards is needed to further reduce infant infection. In areas with a high community level of HIV infection among injection drug users, methadone programs often incorporate HIV primary health care services into the treatment program through onsite services or linkages to services nearby. These services often include obstetrical care by providers skilled in working with HIV-infected women (Finnegan et al., 1993).

**Differences Between Men and Women in HIV Infection Rates and Risk Behaviors**—Figure 22 illustrates that overall HIV infection rates are roughly the same for males and females entering drug abuse treatment in the United States: 5.4 percent for males and 4.4 percent for females. These rates vary greatly (0 to 48 percent) by geographic area, with the highest rates found in urban centers that have the greatest density of injection drug users (Allen, Onorato, and Green, 1992).



**Figure 22 illustrates that overall HIV infection rates are roughly the same for men and women entering drug abuse treatment in the United States: 5.4 percent for men and 4.4 percent for women. These rates vary greatly (0 to 48 percent) by geographic area, with the highest rates found in urban centers that have the greatest density of injection drug users (Allen et al., 1992).**

In research conducted in New York, NY, among 452 methadone-recruited injection drug users early in the HIV epidemic, having an injection drug user as a sex partner was associated with HIV infection status independent of or in addition to injection risk behavior. In this same study, women reported a higher level of sexual risk behavior than men: 57 percent of women compared with 45 percent of men reported one or more injection drug users as sex partners since 1978. In addition, women were more likely than men to have engaged in sex work: 23 percent of women compared with 5 percent of men (Schoenbaum, Hartel, Selwyn, et al., 1989).

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## Question 9: Is methadone maintenance treatment effective for women?

**Answer:** Yes. Since the earliest methadone maintenance treatment programs in the United States, women have been treated successfully with methadone through all phases of their lives, including pregnancy. There is consensus that the major outcomes of the effectiveness of methadone maintenance treatment, especially cessation of illicit drug use and lifestyle stabilization, apply to both men and women. However, gender-specific issues, which are often related to the social status of women, are important to treatment effectiveness for female injection drug users.

Compared with men, women are more likely to

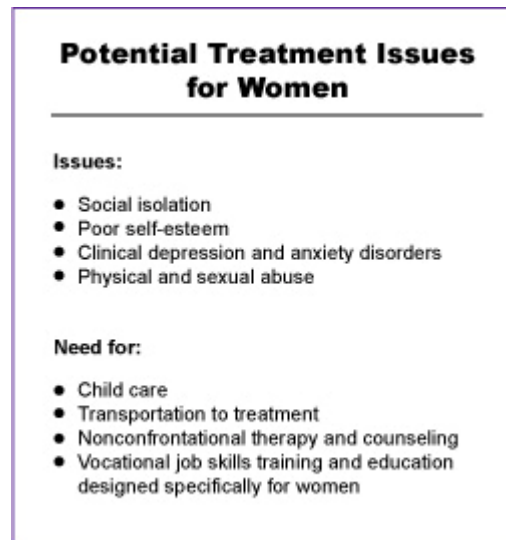
- Have total responsibility for child care
- Have lower socioeconomic status
- Encounter greater barriers to treatment entry, retention in treatment, and economic independence
- Have different psychological, counseling, and vocational training needs
- Have difficulty with transportation to treatment.

### Research Highlights

- In the past, little emphasis was placed on gender-specific biopsychosocial problems in drug treatment. One reason was the predominance of drug-addicted men, estimated in the United States to be three males to every female. Although mild forms of psychoactive substance use show converging usage rates and patterns for males and females, opioid addiction and other forms of chemical dependency continue to show a male predominance (Kandel, 1992).
- Drug Abuse Reporting Program (DARP) studies showed that 19 to 28 percent of admissions to drug treatment programs from 1969 to 1973 were women. In 12 years of followup of 84 females and 91 males in methadone maintenance, there were no differences between men and women in overall reduction of opioid use. Women required more government financial assistance and had lower rates of employment than men. Compared with men, women were more likely to enter treatment for health reasons (Simpson, 1990; Marsh and Simpson, 1986).
- A study of 567 methadone-maintained patients in California found overall shorter duration of time from first entry to first discharge from treatment for women compared with men (Anglin, Hser, and Booth, 1987). Factors related to poor retention of women in treatment were likely to be a lack of child care and inadequate social and psychological support from domestic partners and other family members (Rosenbaum, 1981; Murphy and Irwin, 1992).
- A study of white, Latina, and African American women in methadone maintenance found that, in general, Latinas were more likely to report familial influences and to display evidence of low self-esteem and self-efficacy, inconsistent condom use, and high-risk injection behavior. White women reported the highest levels of regular condom use at followup; however, they were the least likely to report safer injection practices. African American women expressed the highest levels of self-esteem, yet they reported more alcohol use at intake and crack cocaine use both before and after treatment entry. African American women showed the greatest gains in adopting safer injection practices and were the least likely to report multiple sex partners after treatment entry (Grella, Annon, and Anglin, 1995).
- Drug-using women are likely to experience clinical depression, anxiety disorders, and low self-esteem to a much greater degree than their male counterparts. Women entering treatment have experienced unique gender-specific life events. In particular, female drug users often have been abused physically, sexually, and emotionally. Experiences of sexual violence, especially during childhood, have profound, lifelong psychological effects and often underlie addiction, complicating successful recovery. Methadone maintenance treatment of women requires

awareness of these issues and appropriate counseling. Confrontational styles of therapy and counseling are not effective for most women in treatment (Mondanaro, 1987; Marsh and Miller, 1985; Beschner, Reed, and Mondanaro, 1981; Hartel, 1989/1990).

**Potential Treatment Issues for Women**—Figure 23 delineates key treatment issues derived from the discussion above.



**Figure 23 illustrates the potential treatment issues for women.**

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## Question 10: Is methadone safe for pregnant women and their infants?

**Answer:** Yes. Since the early 1970s, methadone maintenance treatment has been used successfully with pregnant women. There is consensus that methadone can be safely administered during pregnancy with little risk to mother and infant. Maintenance on methadone is necessary to prevent relapse to illicit opioid use and thus to maintain optimal health during pregnancy.

### Research Highlights

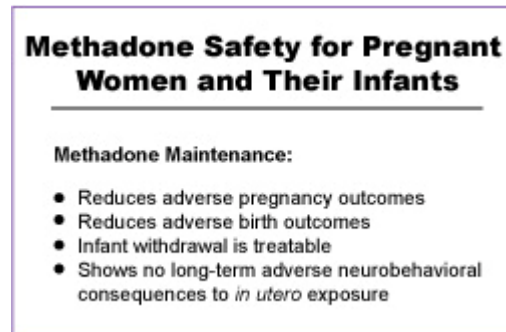
A systematic review revealed that randomized controlled studies of methadone treatment in pregnancy demonstrate an approximate threefold reduction in heroin use and a threefold increase in retention in treatment relative to nonpharmacologic treatment (Rayburn and Bogenschutz, 2004).

- All drug-using women are considered to be at higher-than-normal risk for medical and obstetrical complications. Methadone-maintained women show a far greater improvement in obstetrical health than untreated women. Hepatitis types A, B, and C and other sexually transmitted diseases; bacterial endocarditis; septicemia; and cellulites are common among active injection drug users, particularly those who share needles. Women maintained on methadone who have stopped illicit drug use and injection before pregnancy are less likely to experience these and other medical complications during pregnancy. Obstetrical complications such as spontaneous abortion, placental insufficiency, and other conditions also occur at a lower rate among methadone-maintained women than among opioid-dependent women not enrolled in treatment. When compared with opioid-addicted women not in treatment, women in methadone maintenance treatment have been observed to maintain better overall health and nutritional status during pregnancy because of stability provided through treatment. In addition, methadone clinics can provide onsite prenatal services or link patients to these services in nearby clinics, coordinating addiction treatment and prenatal care to optimize both (Finnegan, 1991; Kaltenbach, Silverman, and Wapner, 1993).
- Some women in methadone maintenance treatment are infected with HIV before pregnancy. Treatment programs that link women to appropriate medical care during pregnancy may reduce the burden of illness suffered by HIV-infected women. In a study of 191 methadone-maintained women in a New York City clinic with extensive medical linkages, medical and obstetrical complications did not differ among women with and without HIV infection. HIV infection occurred among 37 percent of women, most of whom were asymptomatic for HIV disease and AIDS before pregnancy. Adverse birth outcomes were relatively infrequent and occurred at approximately the same rates as observed in studies of methadone-maintained women before the HIV epidemic (Selwyn, Schoenbaum, Davenport, et al., 1989).
- U.S. research in the 1970s demonstrated that methadone does cross the placenta. Passive exposure to methadone in utero can result in neonatal abstinence syndrome among exposed infants. The syndrome varies considerably and depends on a number of factors, including the use of other drugs during pregnancy, anesthesia during delivery, the maturational and nutritional status of the infant, and other aspects of maternal health that affect the fetal environment. The relationship of maternal methadone dose in the last trimester of pregnancy has been explored in a number of studies, but results have not consistently delineated a dose-response relationship between maternal dose and severity of infant abstinence syndrome. For those neonates experiencing withdrawal, the length and severity of the withdrawal vary greatly; however, pharmacotherapy for neonatal methadone abstinence syndrome is simple and effective. Methadone maintenance treatment affords protection of the fetus from erratic maternal opioid levels and repeated episodes of withdrawal typically seen in users of illicit opioids (Finnegan, 1991).

- The majority of infants exposed to methadone in utero are healthy and have fewer adverse outcomes than infants exposed to heroin and other illicit drugs. Methadone maintenance treatment for pregnant women can reduce in utero growth retardation and neonatal morbidity and mortality, in comparison with women not in treatment (Finnegan, 1991). Such infants may be smaller at birth than nondrug-exposed infants, but differences tend to disappear over time. A careful review of the major studies of long-term neurobehavioral effects of methadone on exposed infants revealed no methadone-associated adverse effects (Kaltenbach and Finnegan, 1984).

A review of the literature on methadone and lactation reveals that the amount of methadone in breast milk is very small and depends on the dose of methadone that a mother is receiving. The amount of methadone received by an infant from breast milk is not enough to prevent neonatal abstinence syndrome. Therefore, even though a mother is receiving methadone, her infant may require additional opiate treatment of neonatal abstinence syndrome (Jansson, Velez, and Harrow, 2004).

**Methadone Safety for Pregnant Women and Their Infants**—Figure 24 outlines key points discussed in the research citations above regarding the safety of methadone maintenance treatment for pregnant women.



**Figure 24 illustrates the safety of methadone maintenance treatment for pregnant women and their infants.**

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### **Question 11: Is it necessary to reduce methadone dose or detoxify women from methadone during pregnancy to protect the fetus?**

**Answer:** No. Women have been safely maintained on stable methadone dosage during pregnancy without adverse long-term effects on their health and the health of their infants. Withdrawal of medication during pregnancy leads to opioid abstinence syndrome, which is harmful to the pregnancy and often leads to relapse to illicit drug use. Dosage change in pregnancy must be carefully evaluated on an individual basis. Some women experience lowered blood levels of the methadone during pregnancy and may need an increase in dosage or split (e.g., twice daily) dosing. It is important to determine the relapse risk for each woman when considering a dosage change because a woman steadily maintained on methadone is more likely to have a healthy pregnancy and infant than a woman who uses alcohol and other drugs. The intermittent periods of withdrawal that typically occur with illicit opioid use and can adversely affect the fetus do not occur when methadone is individually determined and properly administered.

### **Research Highlights**

- Optimal methadone dosage for pregnant women in methadone maintenance treatment should be based on careful consideration of risks and benefits to both mother and fetus on an individual basis. Individual dose should be evaluated, taking into account the stage of pregnancy, the relapse risk potential of the mother, pre-pregnancy methadone dose, previous experience with methadone, and history of addiction recovery. When the mother does not relapse to illicit drug use, short-term reductions in maternal dose have been effectively administered during the last stage of pregnancy. However, many women in treatment have been successfully maintained on a constant dose and, in some cases, on an increased dose to keep blood levels stable throughout pregnancy (Finnegan, 1991).
- Some women in treatment experience decreased blood levels of methadone during pregnancy, causing withdrawal symptoms. This decrease in blood levels of methadone during pregnancy can be accounted for by an increased fluid space, a large tissue reservoir that can store methadone, and drug metabolism by both the placenta and the fetus. Pregnant women in treatment with low blood levels of methadone frequently experience a high level of discomfort, withdrawal symptoms, and drug craving and anxiety and may be at high risk of relapse to opioid use and treatment dropout. Determination of methadone blood levels and possibly raising the methadone dosage to maintain sufficient blood levels may be warranted in such cases but must be carefully evaluated. Dosages should be evaluated in conjunction with ongoing medical monitoring of the pregnancy. Since the greatest risks to maternal and infant health occur when women in treatment relapse to illicit drug use, it is important to promote methadone dosage stability during and after pregnancy to optimize both maternal and child health (Kreek, Schecter, Gutjahr, et al., 1974; Pond, Kreek, Tong, et al., 1985).

**Methadone Dosage Adjustment During Pregnancy**—Figure 25 outlines the three main considerations regarding dosage for pregnant women in methadone maintenance treatment.



### **Methadone Dose Adjustment During Pregnancy**

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- Pregnancy can lower methadone blood levels.
- Lower blood methadone levels can increase relapse risk.
- Dosage levels should be evaluated and individually tailored to reduce risk of relapse and to stabilize both mother and fetus.

**Figure 25 illustrates three main considerations regarding methadone dosage adjustment during pregnancy.**

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## **Question 12: Is the long-term use of methadone medically safe, and is it well tolerated by patients?**

**Answer:** Yes. Studies of the long-term administration of methadone confirm that it is a medically safe drug. Long-term methadone maintenance treatment at doses of 80 to 120 mg per day is not toxic or dangerous to any organ system after continuous treatment for 10 to 14 years in adults and 5 to 7 years in adolescents.

### **Research Highlights**

- Methadone has few adverse biological effects. There appear to be no dangerous or troubling psychological effects from long-term administration (Kreek, 1979; Lowinson, Marion, Joseph, et al., 1992), although one study demonstrated a delay in neuropsychological tests in patients receiving methadone compared with abstinent (not active) former heroin-dependent patients (Verdejo, Toribio, Orozco, et al., 2005).
- Methadone sometimes causes minor side effects, such as sweating, constipation, temporary skin rashes, weight gain, water retention, and changes in sleep and appetite (Jaffe and Martin, 1985; Kreek, 1979). These side effects are more likely to occur when the methadone dosages are first being established in a patient, and the side effects generally subside or diminish over time. They can be reduced or eliminated by raising or lowering the methadone dose (Lowinson et al., 1992).
- Methadone prescribed in high doses for a long period of time has no toxic effects and only minimal side effects for adult patients maintained in treatment for up to 14 years and for adolescent patients treated for up to 5 years (Hartel, 1989/1990; Kreek, 1978).
- Although early studies demonstrated no persisting abnormalities directly attributable to methadone in the functioning of five organ systems (pulmonary, cardiovascular, renal, ophthalmologic, and liver) (Kleber, Mezritz, and Slobetz, 1980), later reports have focused on the potential effect of methadone on QTc interval (Martell, Arnsten, Krantz, et al., 2005) and central sleep apnea (Wang, Teichtahl, Drummer, et al., 2005). It should be noted, however, that cardiac complications with methadone are more commonly seen in patients who are prescribed very high doses (mean doses greater than 350 mg per day) for treatment of pain and those who are receiving concomitant medications that affect methadone metabolism (Krantz, Lewkowicz, Hays, et al., 2002).
- Patients maintained on methadone have no impairment in driving and have no more frequent motor vehicle accidents than people not receiving methadone maintenance treatment (Maddux, Williams, and Ziegler, 1977; Lenne, Dietze, Rumbold, et al., 2003; Schindler, Ortner, Peternell, et al., 2004).
- The most common and enduring complaints after 6 months to 3 years of continuous methadone treatment are sweating, constipation, abnormalities in libido and sexual functioning, sleep abnormalities (insomnia and nightmares), and altered appetite (mild anorexia, weight gain) (Kreek, 1979; Jaffe and Martin, 1985). Most of these symptoms can be medically managed (Kreek, 1979). A study of 92 methadone-maintained patients found that the rate of global sexual dysfunction in methadone-treated men was similar to the general population but that orgasm dysfunction may respond to methadone dose reduction.
- Although euphoria and drowsiness, with occasional nausea and vomiting, can occur before tolerance develops, these side effects are most noticeable when doses are increased too rapidly. Conversely, if a heroin habit has been particularly heavy, initial methadone doses may be too low to prevent the onset of early withdrawal symptoms (Kreek, 1979).

- Life-threatening interactions of methadone with other drugs have not been identified. Drugs found to affect the metabolism of methadone include phenytoin (Dilantin) and rifampin. Opioid antagonists such as pentazocine (Talwin) and buprenorphine can cause withdrawal symptoms in methadone patients and should not be prescribed (Kreek, 1978).

Common Side Effects After 6 Months to 3 Years of Methadone Maintenance Treatment		
Symptoms and Signs	Intermediate Length Treatment (6 Months or More; <40 to >80 mg/d)	Long-Term, High-Dose Treatment (3 Years or More; 80 to 120 mg/d)
	Percent	Percent
Increased Sweating	47	48
Constipation	57	17
Libido Abnormalities	26	22
Orgasm Abnormalities	—	14
Sleep Abnormalities (Insomnia)	23	16
Appetite Abnormalities	19	4
Nausea	25	—
Drowsiness	23	—
Nervousness/Tension	21	—
Headaches	12	—
Body Aches and Pains	11	—
Chills	10	—
— = no data available		

**Figure 26 illustrates that methadone maintenance patients, in the early stages of treatment, can experience several minor side effects: sweating, constipation, orgasm abnormalities, alterations of sexual interest, alterations of sleep and appetite, nausea, drowsiness, nervousness, headaches, body aches and pains, and chills. However, the figure also shows that many of these side effects almost disappear with long-term, high-dose methadone maintenance treatment (Kreek, 1979; Jaffe and Martin, 1985; Hartel, 1989/1990).**

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### **Question 13: Are there program characteristics associated with the success of methadone maintenance treatment?**

**Answer:** Yes. There are several program characteristics associated with a variety of improved treatment outcomes in patients receiving methadone maintenance. These program characteristics are as follows:

- Establishment of evidence-based dosing policies and dose ranges
- Availability of a variety of psychosocial services for those who require them
- Attention to staff training and quality
- When possible, integration of medical, counseling, and administrative services

### **Research Highlights**

- A meta-analysis of 12 trials involving 981 people comparing varying levels of psychosocial treatment added to methadone maintenance showed additional benefit in adding any psychosocial treatment to standard methadone maintenance treatment in relation to the use of heroin during the treatment; relative risk was 0.69 (95% CI 0.53 to 0.91). However, no statistically significant additional benefit was shown in terms of retention in treatment—relative risk was 0.94 (95% CI 0.85 to 1.02)—or proportion of patients retained or abstinent at followup—relative risk was 0.90 (95% CI 0.76 to 1.07) (Amato, Minozzi, Davoli, et al., 2004).
- Ball and Ross (1991) noted wide differences among the six methadone maintenance clinics studied with respect to the reduction of injection drug use by patients. Factors that account for treatment success include (1) adequate dosing; (2) participation in programs that had high retention rates, high rates of scheduled attendance, low treatment staff turnover, and a close, consistent, and enduring relationship between staff and patients; (3) an effective treatment director; (4) combined medical, counseling, and administrative services; (5) experienced counselors providing comprehensive counseling services; and (6) staff/patient agreement about the status of patients and their treatment needs.
- In a United Kingdom study of 262 patients who were admitted to and retained in methadone treatment programs at 6 months, structural equation models were used to evaluate relationships between treatment process variables and heroin use at 1 and 6 months. Patients' perceptions of program characteristics and methadone dose were related to reduced heroin use at 1 month. In addition, early engagement with treatment services was associated with decreased heroin use at 6 months (Gossop, Stewart, and Marsden, 2003).
- Studies comparing methadone treatment in general practice or primary care with treatment in specialty treatment clinics are limited, but at least two have demonstrated similar treatment outcomes between these two locations of care (Gossop, Marsden, Stewart, et al., 1999; Fiellin, O'Connor, Chawarski, et al., 2001).
- The Treatment Outcome Perspective Study (TOPS) examined a sample of 606 methadone maintenance treatment patients from 21 different clinics to identify treatment process factors related to improved patient retention rates. Results showed higher patient retention rates for programs (1) using organized and professional staff to diagnose problems and define treatment plans, (2) meeting and satisfying the needs perceived as important by clients, and (3) using higher methadone doses (Joe, Simpson, and Hubbard, 1991).
- A 6- to 7-year followup study of 347 methadone maintenance treatment patients examined different retention policies. Two programs had a high-dose, long-retention policy in which involuntary termination was used as a last resort. A third program had a low-dose, 2-year retention policy with strict terminations for program violations. Retention rates were longer in the two less structured programs (means of 4.3 and 3.2 years) than in the more structured program (mean of 2.2 years) (McGlothlin and Anglin, 1981).

- One study randomly assigned 69 patients at admission to structured and unstructured treatment groups. Structured groups had limits on illicit drug use that, if exceeded, resulted in withdrawal from methadone. The unstructured groups had no limits on illicit drug use. At the end of 1 year, 53 percent of the patients in structured groups remained in treatment, but only 30 percent of the patients in unstructured groups remained in treatment (McCarthy and Borders, 1985).
- A nationwide U.S. telephone survey of a randomized and stratified representative sample of 172 outpatient methadone units found that relatively high methadone dosage levels and patient participation in dosage decisions are related to higher retention rates (D'Aunno and Vaughn, 1992).
- According to Kreek (1991), adequate staff numbers, training, and concern for patient needs and high staff stability (low staff turnover) are associated with improved patient outcomes (Center for Substance Abuse Treatment, 1993).

**The Effects of Dosage on Methadone Maintenance Treatment**—Research regarding methadone dosage levels clearly establishes that low average doses are inappropriate in methadone maintenance treatment. No single level is effective for all patients, although NIDA-supported research has suggested that the minimum effective dosage for most methadone maintenance patients is 60 mg per day. The specific dosage for a patient cannot be determined arbitrarily because patients metabolize methadone at different rates. In addition, the appropriate dosage can change over time or in response to specific situations such as pregnancy or the use of other medications. Overall, methadone dosage should be based on the patient's individual needs, goals of treatment, and progress in treatment.

In the Ball and Ross studies (1991), illicit opioid use was directly related to methadone dosage levels. In methadone maintenance patients on dosages of about 71 mg per day, no heroin use was detected, but methadone maintenance patients on dosages below 46 mg were 5.16 times more likely to use heroin than those on higher dosages.

Ball and colleagues (1988) found that 18.6 percent of 490 patients who were in methadone maintenance treatment for 6 months to 4.5 years used heroin within the last 30 days, but use correlated strongly with methadone dosage level. At doses of 75 mg per day and above, the continuing use of heroin stopped altogether. In contrast, 64 percent of patients maintained on 10 mg per day or less continued frequent heroin use. A dose of 40 mg per day seemed to be the cutoff point for a large decrease in heroin use.

Despite recent attention to the importance of adequate methadone dosages, a large-scale survey of methadone maintenance treatment programs conducted in the United States in 1992 found that 50 percent of patients nationwide receive suboptimum methadone doses (D'Aunno and Vaughn, 1992). A subsequent evaluation found that the percentage of patients receiving methadone doses less than 60 mg per day has decreased from 79.5 percent in 1988 to 35.5 percent in 2000. Programs with a greater percentage of African American patients were more likely to dispense low doses of methadone, and programs with Joint Commission on Accreditation of Healthcare Organizations accreditation were more likely to provide adequate methadone doses (D'Aunno and Pollack, 2002).

In an exhaustive review of 22 studies that compared the effects of different methadone dosages on outcomes such as patient retention, continuing illicit opioid use, and symptoms, Hargreaves (1983) concluded that daily methadone doses of 100 mg were superior to those of 50 mg during the first 5 to 10 months of methadone maintenance treatment for a sizeable subgroup (10 percent to 30 percent) of opioid addicts.

In a study of 2,400 patients enrolled in methadone maintenance over a 15-year period, those patients maintained on a daily dose of 60 mg or more had longer retention in treatment; less use of heroin and

other drugs, including cocaine; and a lower incidence of HIV infection and AIDS (Hartel, Selwyn, and Schoenbaum, 1988a and 1988b).

In a multiclinic study of 12 Veterans Administration hospitals, methadone maintenance treatment patients were assigned to two dosage levels of methadone: 50 mg and 100 mg. The percentage of patients retained for 10 months was higher in the 100-mg group (52 percent) than in the 50-mg group (42 percent), but the difference was not statistically significant (Ling, Charuvastra, Kaim, et al., 1976).

Studies that examined the relationship between methadone maintenance treatment dosage and retention suggest that, although many patients will continue in treatment on methadone doses of less than 50 mg, some patients need higher doses. In a review of five well-designed dose-retention studies, three found statistically nonsignificant trends toward increased retention with higher doses and two did not (Maddux, Vogtsberger, Desmond, et al., 1993).

In a study of 180 methadone maintenance treatment patients randomly assigned at admission to three groups that received doses of 30 mg, 50 mg, and 100 mg, the percentages retained for 53 weeks were as follows: 45 percent of the 30-mg group, 55 percent of the 50-mg group, and 35 percent of the 100-mg group. The 100-mg group had the lowest retention rate, but the differences were not statistically significant (Garbutt and Goldstein, 1972).

A study of 322 methadone maintenance treatment patients receiving an average daily dose of 30 mg demonstrated a high dropout rate. Only 17 percent of the sample remained in treatment at the end of 6 months, and only 10 percent remained by the end of a year. Moreover, patients who dropped out within the first 30 days had the same drug-using behavior as they did before treatment (Craig, 1980).

Methadone dose should not be rapidly increased or decreased—or used in contingency management—because such changes tend to disrupt the normalization of physiological function achieved by steady dose treatment. If the stabilized methadone dose/plasma levels are disrupted, drug hunger and drug-seeking behaviors are likely to reappear (Kreek, 1991; Kreek, 1992).

**Need for Comprehensive Services in Methadone Maintenance Treatment**—In a study of 351 daily or weekly heroin users who were admitted to 1 of 17 publicly funded methadone maintenance treatment programs, nearly all (85 percent) reported having difficulty in at least one of the following problem areas: medical or physical; mental health or emotional; family or friends; police or legal; job, work, or school; and financial or money. Nearly one-half (44 percent) reported having difficulties in more than three of these areas (Condelli, 1993).

**Program Characteristics Associated With Success of Methadone Maintenance Treatment**—Other program characteristics that appear to improve treatment success include having sufficient staff, low staff turnover and high staff stability, sufficient staff training, and close and enduring relationships between staff and patients.



### Program Characteristics Associated With Success of Methadone Maintenance Treatment

#### Successful programs have:

- Comprehensive services
- Integrated medical, counseling, and administrative services
- Individualized treatment
- Adequate dosing policies
- Sufficient and stable staff
- Sufficient staff training

Figure 27 illustrates the program characteristics, identified by numerous research studies, that contribute to methadone maintenance treatment success (McLellan, Arndt, Metzger, et al., 1993; Ball and Ross, 1991; Joe et al., 1991).

### Role of Psychological Services in Reducing Illicit Opioid Use

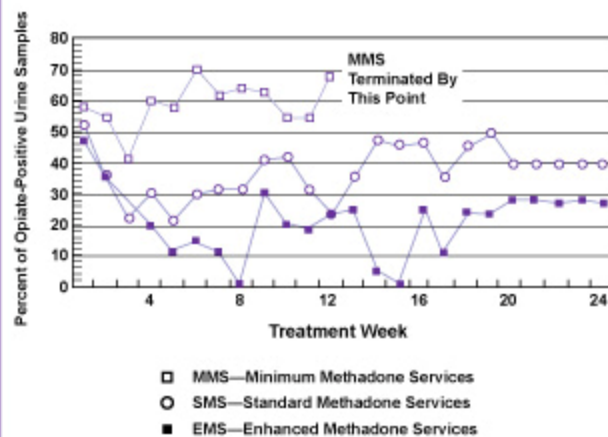


Figure 28 illustrates that in a recent study, 102 patients were divided into three groups: (1) minimum methadone maintenance treatment services (methadone alone); (2) standard methadone maintenance treatment services (methadone plus counseling); and (3) enhanced methadone maintenance treatment services (methadone, counseling, and onsite medical, psychiatric, employment, and family therapy services). At 24 weeks, methadone alone resulted in minimal improvements; methadone plus counseling resulted in significant improvements over methadone alone; and enhanced Services, including a broad range of psychosocial services plus methadone, had the best outcomes of all (McLellan et al., 1993). Patients receiving the most comprehensive array of treatment services were the most likely to have opioid-free urine tests for the 24 weeks of the study. Patients receiving minimal services were the most likely to have urine tests that were positive for illicit opioids. Note: These patients were removed from participation in the study because of drug use and psychiatric difficulties. Additional treatment services were made available.

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#### **Question 14: Are there patient characteristics associated with the success of methadone maintenance treatment?**

**Answer:** Yes. Patient characteristics associated with treatment success include the following:

- Age
- Age of first heroin use
- Overall drug-use history
- Severity and duration of drug use
- Emotional health
- Psychiatric health
- Social health
- Vocational stability
- Criminal history

#### **Research Highlights**

One review found the following characteristics to be associated with improved methadone outcomes: older age, absence of criminal behavior, shorter duration of opioid use, less severe psychopathology, being employed, being married, less polysubstance use, and higher expressed desire in getting help with a drug problem (Ward, Mattick, Hall, et al., 1998).

- In a review of 113 studies that attempted to evaluate the relationship of patient characteristics to retention and other outcomes (reported from 1971 to 1983), it was noted that patient characteristics probably accounted for only 25 to 45 percent of the variance in retention (McLellan, 1983).
- For methadone maintenance treatment patients in the Drug Abuse Reporting Program (DARP) studies, the most important predictors of posttreatment outcomes were (1) preadmission criminality and (2) measurements of crime, drug use, and employment during treatment. Of all the patient characteristics, chronic criminality is the strongest predictor of unfavorable posttreatment outcomes (Simpson and Sells, 1982).
- Ball and Ross's work (1991) supports the finding that a younger age at the onset of heroin use is associated with poorer treatment outcomes. Overall, however, this study noted that patient characteristics had less impact on outcomes than program variables.
- Anglin and Hser (1990) note that better psychosocial adjustment predicts superior treatment outcomes. Psychosocial adjustment was described as an intact marriage, a job, a shorter history of drug abuse, lower levels of psychiatric dysfunction, and minimal or no criminal history.
- Rounsaville, Glazer, Wilber, et al. (1983) assessed 123 opioid addicts who were followed for 6 months after admission and found that outcome was predicted by the behavior examined: greater pretreatment criminality predicts criminal activity following discharge. Conversely, pretreatment employment predicts posttreatment employment. This study found that patients who abuse alcohol, are unemployed, are dually diagnosed, manifest psychopathology, and engage in criminality have poor outcomes.

### **Patient Characteristics Associated With Success of Methadone Maintenance Treatment**

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- Age: Older than 25
- Minimal criminal involvement
- Short history of drug abuse
- Mild to moderate drug abuse severity
- Emotional and psychiatric stability
- Intact social support network
- Positive employment history

**Figure 29 illustrates that, overall, patients who demonstrate emotional, psychological, and social well-being generally experience greater treatment success than patients who have emotional, psychological, and social problems. Several studies have noted that certain patient characteristics, which are listed in Figure 29, are associated with success in methadone maintenance treatment (McLellan, 1983; Simpson and Sells, 1982; Ball and Ross, 1991; Anglin and Hser, 1990).**

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## Question 15: Are there cost benefits to methadone maintenance treatment?

**Answer:** Yes. Research has demonstrated that methadone maintenance treatment is beneficial to society, cost-effective, and pays for itself in basic economic terms.

### Research Highlights

A cost-effectiveness analysis reviewed five policy questions from an economic perspective: (1) whether methadone should be a healthcare benefit; (2) what level of ancillary services is optimal; (3) what methadone dose is appropriate; (4) what length of treatment is appropriate; and (5) whether contingency contracts should be employed. The analysis found that expanded access to methadone maintenance had an incremental cost-effectiveness ratio of less than \$11,000 per quality-adjusted life year (QALY). Ancillary services were shown to be an effective part of methadone maintenance therapy, especially during the beginning of a treatment episode. The cost of additional methadone was found to be low compared with the benefits of adequate doses. Short episodes of methadone maintenance were felt not likely to be cost-effective (Barnett and Hui, 2000).

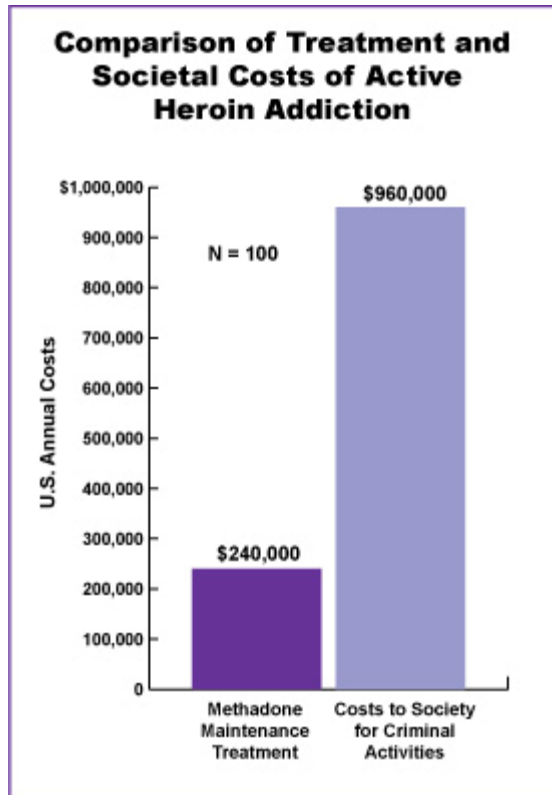
A unique and timely analysis was performed that focused on the cost-effectiveness of methadone treatment based on its impact on the HIV epidemic. The analysis considered populations in which HIV prevalence among injection drug users ranged from 5 percent to 40 percent. The results demonstrated that increased methadone maintenance capacity costs \$8,200 per QALY gained in high-prevalence communities and \$10,900 per QALY gained in low-prevalence communities. Interestingly, the majority of benefits were gained by individuals who do not inject drugs (Zaric, Barnett, and Brandeau, 2000).

- A standard cost-effectiveness evaluation of methadone considered the incremental effect of methadone on the lifespan and treatment cost of a cohort of 25-year-old heroin users. The results demonstrated that providing opioid-dependent patients with methadone maintenance had an incremental cost-effectiveness ratio of \$5,915 per life-year gained. A sensitivity analysis determined that the ratio was less than \$10,000 per life-year over a range of assumptions. This cost-effectiveness ratio was lower than that of many common medical therapies and well within the \$50,000 threshold typically used in developed countries for judging cost-effectiveness (Barnett, 1999).
- A systematic review from Lithuania on studies of the cost-effectiveness of methadone noted that methadone maintenance had higher economic efficiency with daily doses of 80 to 100 mg, and daily doses lower than 40 mg were considered inefficient. In addition, short treatment episodes were not likely to be cost-effective, and ancillary services were more cost-effective at the beginning of methadone maintenance than in the later stages. Economic efficiency was found to be higher as treatment program census increased as opposed to the provision of more ancillary services (Vanagas, Padaiga, and Subata, 2004).
- The most comprehensive examination of economic benefits and costs was performed on data from the Treatment Outcome Perspective Study (TOPS). After examining the average cost of a methadone maintenance treatment day, detailed measurements of criminal activities rates, and the cost to society of various crimes, the study yielded a final benefit-to-cost ratio of 4 to 1 (Harwood, Hubbard, Collins, et al., 1988).
- Rufener, Rachal, and Cruz (1977) studied the cost-effectiveness of methadone maintenance (and other treatment modalities) and determined a benefit-to-cost ratio of 4.4 to 1.
- McGlothlin and Anglin (1981), using data from low-dose programs, compared patients who left methadone maintenance treatment when a community clinic was closed in Bakersfield, California, with patients in another community's program that remained open. For men, the ratio of crime-related economic benefits to treatment costs was 1.7 to 1 over a 2-year period. In

addition, the continuous treatment group reported significantly higher rates of employment than those who had been closed out of treatment, although the factor was not formally assessed in the study.

- Methadone maintenance treatment, when implemented at sufficient resource levels, provides individual and social benefits for at least several years that are substantially higher than the cost of delivering this treatment. The daily benefits equal the daily costs in virtually every case, even among those who continue drug use at a reduced level (Gerstein and Harwood, 1990).
- There are many more costs to society associated with active heroin use (Rufener et al., 1977). These include medical costs, law enforcement costs, judicial system costs, corrections costs, nondrug crime costs, drug traffic control, drug abuse prevention costs, reducing housing stock costs, absenteeism costs, unemployment costs, and drug-related deaths. Thus, when all costs to society are considered, methadone maintenance treatment is extremely cost-effective and beneficial to society.
- A study that randomly assigned new patients to three levels of care (methadone alone, methadone plus standard counseling services, and methadone plus enhanced services [counseling, medical/psychiatric, employment, and family therapy services]) found that methadone plus standard counseling was most cost-effective. At 12 months, the annual cost per abstinent client was \$16,485, \$9,804, and \$11,818 for the low, intermediate, and high levels of counseling, respectively (Kraft, Rothbard, Hadley, et al., 1997). A similar finding was obtained in a cost-effectiveness study of varying levels of care provided along with methadone maintenance in Spain (Puigdollers, Cots, Brugal, et al., 2003).
- In a study comparing ongoing methadone maintenance with 6 months of methadone maintenance followed by detoxification, total healthcare costs were greater for maintenance than detoxification treatment (\$7,564 vs. \$6,687;  $p < 0.001$ ). However, detoxification patients incurred significantly higher costs for substance abuse and mental healthcare services. Methadone maintenance appeared to provide a small survival advantage compared with detoxification. The cost per life-year gained was \$16,967. Sensitivity analysis revealed a cost-effectiveness ratio of less than \$20,000 per QALY over a range of modeling assumptions (Masson, Barnett, Sees, et al., 2004).

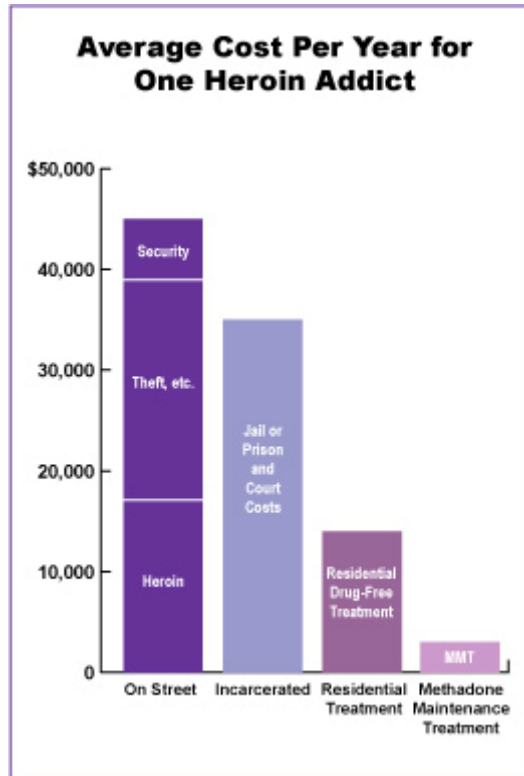
**Comparison of Treatment and Societal Costs of Active Heroin Addiction**—A study of the cost benefits of methadone maintenance treatment showed that the costs to society of the criminal activities related to active heroin use can run as high as four times more than the costs for methadone maintenance treatment (Harwood et al., 1988).



**Figure 30 illustrates the cost-benefit relationship. For example, if the approximate annual cost for providing methadone maintenance treatment is \$2,400 per person, it would cost about \$240,000 to provide treatment for 100 patients for 1 year. In contrast, the annual costs to society related to the criminal activities of 100 active heroin addicts not in treatment would exceed \$960,000 (Harwood et al., 1988).**

Through the New York State Department of Substance Abuse Services, NIDA researchers have estimated the yearly cost to maintain an opioid addict in New York: untreated and on the street (\$43,000), in prison (\$34,000), in a residential drug-free program (\$11,000), and in methadone maintenance treatment (\$2,400) (New York State Committee of Methadone Program Administrators, 1991).





**Figure 31 illustrates the cost of active heroin use for one addict for a year at about \$43,000 in 1991. This includes the cost of the heroin, the loss of property related to theft and burglary, and the costs of security measures to combat such crimes.**

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## Question 16: What are the retention rates for methadone maintenance treatment?

**Answer:** Retention in methadone is related to the dose of methadone but not the provision of ancillary services.

### Research Highlights

- A meta-analysis of studies comparing the provision of methadone maintenance with and without ancillary services demonstrated decreased illicit heroin use with ancillary services but found no statistically significant additional benefit in terms of retention in treatment, RR 0.94 (95% CI, 0.85 to 1.02) (Amato, Davoli, Perucci, et al., 2005).
- An observational study of 351 patients in the United Kingdom receiving methadone maintenance compared with those receiving methadone dose reduction found the following retention rates: 88 percent vs. 86 percent at 1 month, 71 percent vs. 58 percent at 2 months, 62 percent vs. 50 percent at 1 year, and 42 percent vs. 30 percent at 2 years (Gossop, Marsden, Stewart, et al., 2001).
- An Italian study followed 1,503 heroin-dependent patients who received treatment in the form of methadone maintenance, a drug-free program, or naltrexone. The retention rate after 1 year was 40 percent for patients in methadone maintenance, 18 percent in naltrexone, and 15 percent in the drug-free program. Patients receiving methadone greater than or equal to 60 mg per day and 30 to 59 mg per day were respectively 70 and 50 percent more likely to remain in treatment than those receiving less than 30 mg per day. Patients receiving methadone maintenance were 30 percent more likely to remain in treatment than those not receiving methadone (D'Ippoliti, Davoli, Perucci, et al., 1998).
- Thirty-eight percent of the new patient group (total 126) in the Ball and Ross (1991) studies of six methadone maintenance treatment programs remained in treatment after a year; 63 percent of the moderate-stay group (total 345) were still in treatment a year later; and 84 percent of the long-term patients (total 146) continued their methadone maintenance treatment for another year.
- In a study of 311 admissions to three methadone maintenance treatment programs during 1990 and 1991, 24 percent dropped out within 60 days. The significant predictors of retention were social stability (being married, employed, and having few prior arrests); previous treatment experience; high dosage levels; and motivation for treatment (Simpson and Joe, 1993).

### Additional Studies

- In a study of 351 daily or weekly heroin users who were admitted to 1 of 17 publicly funded methadone treatment programs, predictors of retention in methadone maintenance treatment programs included (1) positive patient evaluations of the quality of social services received during the first month after admission (e.g., family, legal, educational, employment, financial services); (2) positive patient ratings of how easily accessible the program was; and (3) participation in programs that informed patients of their methadone dosage levels (Condelli, 1993).

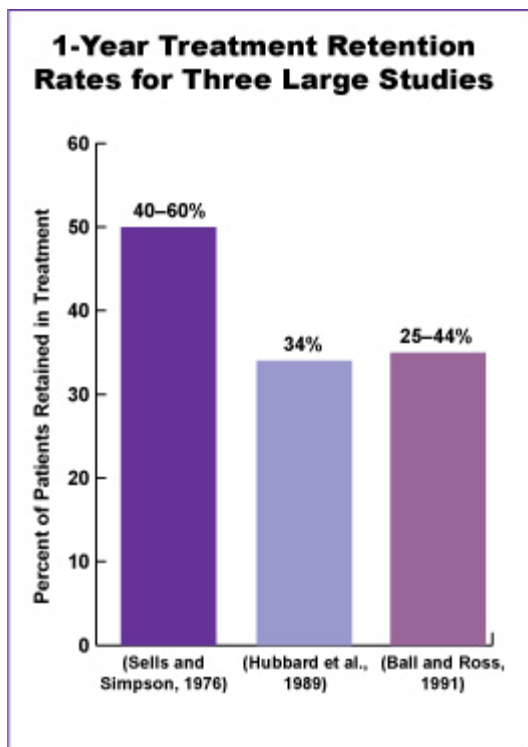


Figure 32 illustrates 1-year treatment retention rates for three large studies.

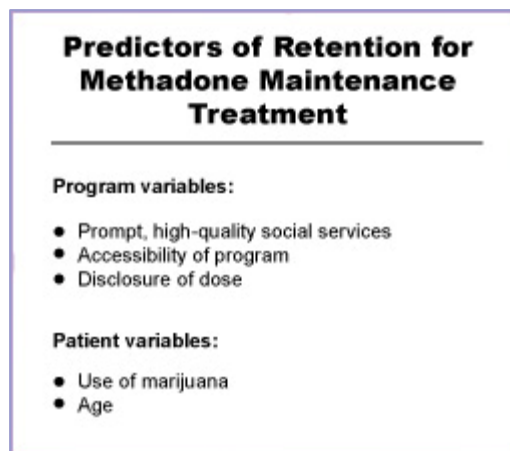


Figure 33 illustrates that in the Treatment Outcome Perspective Study (TOPS), patient self-report ratings of the quality (not the number) of social services received during the first month of methadone maintenance treatment were a strong predictor of retention (Condelli and Duntelman, 1993). The study suggests that methadone maintenance treatment programs should provide patients with high-quality social services as soon as possible after admission in order to promote retention. The study found that three program and two patient variables predicted retention. It also noted that patients who were 25 years of age or younger were more likely than older patients to drop out of methadone maintenance treatment programs, possibly because they lacked the motivation, maturity, and life goals that often characterize older patients.

**Likelihood of Relapse After Leaving Methadone Treatment**—Of 105 patients who were followed in the community after leaving methadone maintenance treatment after 1 month to 1 year or longer, two-thirds (67.6 percent) relapsed to injection drug use (Ball and Ross, 1991).

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### **Question 17: Is mandated methadone maintenance treatment as effective as voluntary treatment?**

**Answer:** Yes. Mandated methadone maintenance treatment (being forced to attend treatment by the criminal justice system) is as effective as voluntary treatment.

#### **Research Highlights**

A study examined the relationship between length of stay in methadone maintenance treatment and referral by legal and nonlegal sources of 2,200 patients. It was determined that patients who are legally referred to methadone maintenance treatment stay in treatment longer than, and do at least as well as, those who seek treatment voluntarily (Collins and Allison, 1983).

A study of 121 male veterans in a 90-day Veterans Administration drug rehabilitation program compared court-referred and voluntary patients. Objective and subjective measures both indicate that the court-referred patient is potentially as responsive to methadone maintenance treatment as the voluntary patient. Sixty-two percent of the court-referred patients were judged to have a good prognosis compared with 58 percent of the voluntary patients (McLellan and Druley, 1977).

Three samples of methadone maintenance treatment admissions, who were treated during the years of 1971 to 1973, participated in a followup study 7 years later. These groups included (1) a random sample of 100 patients, (2) a sample of 136 patients who had a minimum of 30 months remaining on civil addict parole status at the time of admission, and (3) a matched sample of 136 patients not on parole. The addition of parole supervision with urine testing resulted in only marginal improvements in behavior over that attributable to methadone maintenance treatment alone; however, parole status did significantly reduce the length of intervals of daily heroin use both before and after admission (Anglin, McGlothlin, and Speckart, 1981).

**Mandated Methadone Maintenance Treatment and Three Treatment Outcomes**—Patients who are legally coerced into methadone maintenance treatment experience treatment success at about the same rate as patients who participate voluntarily in treatment.

A study by Anglin, Brecht, and Maddahian (1990) examined patients who were mandated to treatment and those who entered voluntarily. One group was forced to participate in methadone maintenance treatment (high coercion). A second group (not represented in Figures 34 through 36) had moderate legal pressure to participate in methadone maintenance treatment (medium coercion). A third group had mild legal pressure to participate in methadone maintenance treatment (low coercion).

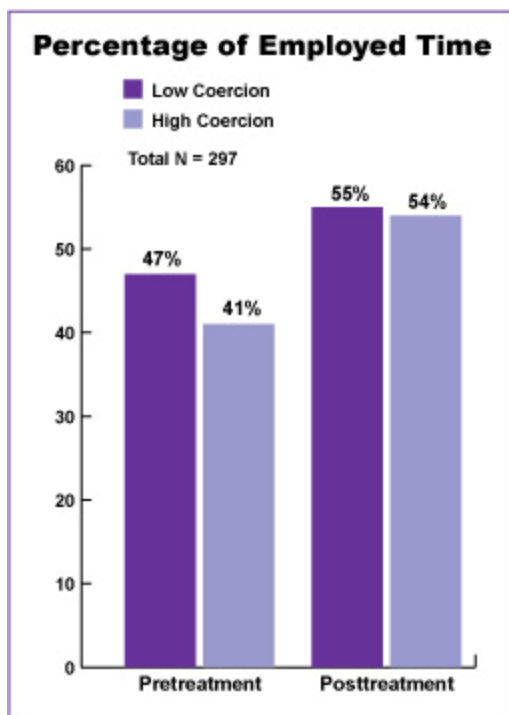


Figure 34 compares the behaviors of individuals in the high-coercion group with those of individuals in the low-coercion group for the treatment outcome of time employed. As the figure illustrates, patients who are coerced in treatment achieve this treatment outcome at about the same rate as patients who voluntarily participate in methadone maintenance treatment (Anglin et al., 1990).

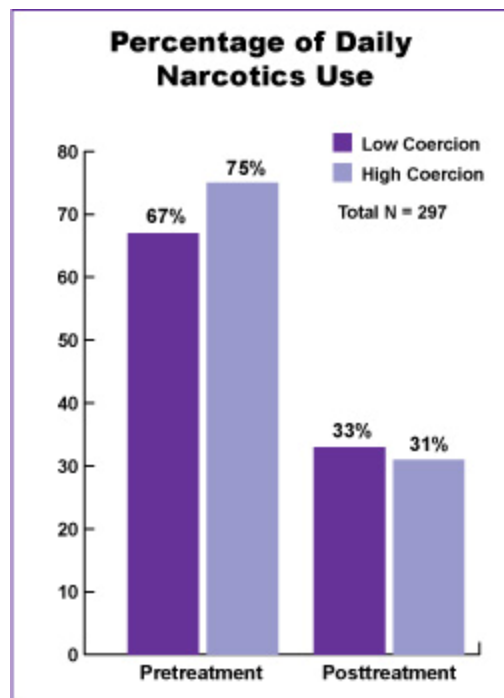


Figure 35 compares the behaviors of individuals in the high-coercion group with those of individuals in the low-coercion group for the treatment outcome of daily narcotics use. As the figure illustrates, patients who are coerced in treatment achieve this treatment outcome at about the same rate as patients who voluntarily participate in methadone maintenance treatment (Anglin et al., 1990).

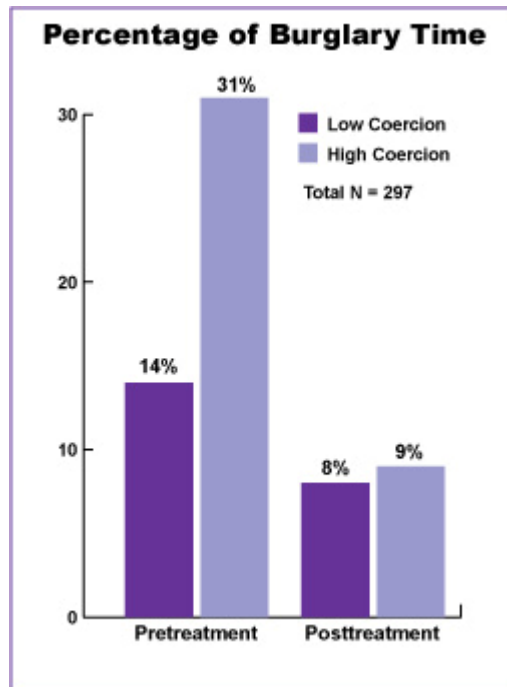


Figure 36 compares the behaviors of individuals in the high-coercion group with those of individuals in the low-coercion group for the treatment outcome of criminal involvement. As the figure illustrates, patients who are coerced in treatment achieve this treatment outcome at about the same rate as patients who voluntarily participate in methadone maintenance treatment (Anglin et al., 1990).

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**Question 18: What is the role of L-alpha-acetyl-methadol (LAAM)?**

**Answer:** L-alpha-acetyl-methadol (LAAM), a potent opioid with a longer duration of action than methadone, can suppress opioid withdrawal for up to 72 hours. Research on both LAAM and methadone maintenance treatment provides comparable results regarding patients' reported clinic attendance, opioid withdrawal symptoms, illicit drug use, employment status, and criminal activity. Both treatments are similar regarding overall effectiveness.

Due to concerns over reports of QT interval prolongation and episodes of Torsades de Point, LAAM was removed from the European markets and subsequently had limited use in the United States.

## Question 19: How do buprenorphine and methadone compare?

**Answer:** Buprenorphine is approved for use in the treatment of opioid dependence in a large number of countries, including Australia, Belgium, Canada, Croatia, Germany, Iran, England, France, the United Kingdom, and the United States. Buprenorphine is a partial agonist at the opioid receptor, as opposed to a full agonist such as methadone or heroin. This means that buprenorphine has a unique pharmacologic profile leading to a lower likelihood of overdose or respiratory depression. Like methadone, buprenorphine has the ability to suppress opioid craving and withdrawal, block the effects of self-administered opioids, retain patients in treatment, and decrease illicit opioid use. Because it is a partial agonist, buprenorphine maintains patients in a milder degree of physical dependence and is associated with milder withdrawal syndrome following cessation.

Clinical trials comparing the efficacy of buprenorphine to methadone on the outcomes of retention and illicit opioid use have demonstrated similar results when compared with low doses of methadone (20 to 30 mg) (Johnson, Jaffe, and Fudala, 1992; Ling, Wesson, Charuvastra, et al., 1996). Comparisons to higher doses (35 to 90 mg) of methadone have yielded mixed results (Strain, Stitzer, Liebson, et al., 1994; Kosten, Schottenfeld, Ziedonis, et al., 1993).

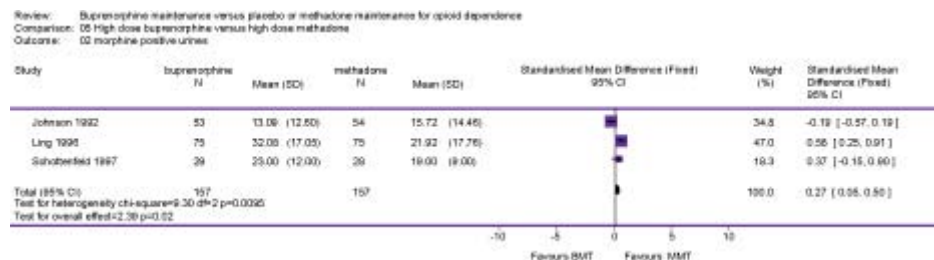


Figure 37a

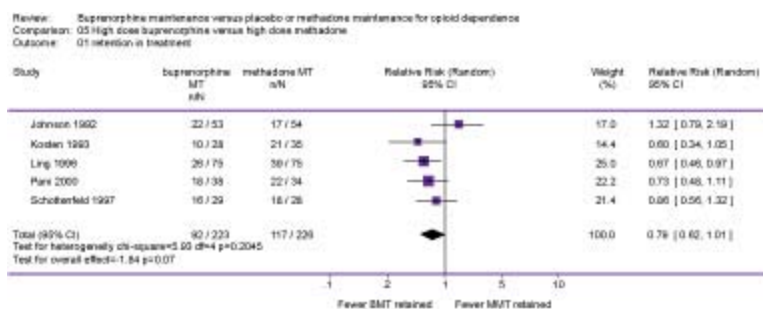


Figure 37b

Figures 37a and 37b illustrate that a meta-analysis of 13 clinical trials that compared buprenorphine maintenance with methadone maintenance had the following findings: “Buprenorphine given in flexible doses appeared statistically significantly less effective than methadone in retaining patients in treatment (RR = 0.82; 95% CI: 0.69-0.96). Low-dose buprenorphine is not superior to low-dose methadone. High-dose buprenorphine does not retain more patients than low-dose methadone, but may suppress heroin use better. There was no advantage for high-dose buprenorphine over high-dose methadone in retention (RR = 0.79; 95% CI: 0.62-1.01), and high-dose buprenorphine was inferior in suppression of heroin use. Buprenorphine was statistically significantly superior to placebo medication in retention of patients in treatment at low doses (RR = 1.24; 95% CI: 1.06-1.45), high doses (RR = 1.21; 95% CI: 1.02-1.44), and very high doses (RR = 1.52; 95% CI: 1.23-1.88). However, only high and very high dose buprenorphine suppressed heroin use significantly above placebo.” (Mattick, Kimber, Breen, et al., 2003.) (Please note, this review will be updated.)

Patients receiving buprenorphine can be either (1) discontinued without significant withdrawal, (2) maintained, or (3) transferred to opioid antagonist treatment, such as naltrexone. Patients with a higher level of physical dependence and whose needs cannot be met by buprenorphine can be transferred to an opioid agonist, such as methadone or L-alpha-acetyl-methadol (LAAM).

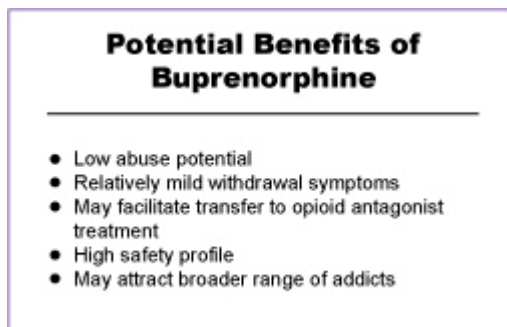
### Research Highlights

- Mello and Mendelson showed that buprenorphine suppresses heroin self-administration by opioid-dependent primates and humans (Mello and Mendelson, 1980; Mello, Mendelson, and Kuehnle, 1982; Mello, Bree, and Mendelson, 1983).
- Findings from a subsequent dose-ranging study at the Los Angeles Addiction Treatment Research Center (LAATRC) suggest that the median doses of buprenorphine for adequate clinical stabilization may be in the 12- to 16-mg range (Compton, Ling, Charuvastra, et al., in press).
- A NIDA-sponsored, 12-site LAATRC/Veterans Administration/NIDA multicenter study compared doses of 1, 4, 8, and 16 mg of buprenorphine in 631 patients. The primary comparison between the 8-mg and the 1-mg groups shows that the 8-mg group used fewer illicit opioids and remained in treatment longer (Ling, Charuvastra, Collins, et al., 1998).

A clinical trial comparing buprenorphine, the buprenorphine/naloxone combination, and placebo was terminated early because buprenorphine and naloxone in combination and buprenorphine alone were found to have greater efficacy than placebo. Opioid-negative urine samples were found more frequently in the buprenorphine and buprenorphine/naloxone groups (17.8% and 20.7%, respectively) than in the placebo group (5.8%,  $p < 0.001$  for both comparisons) (Fudala, Bridge, Herbert, et al., 2003).

### Potential Benefits of Buprenorphine

Research on buprenorphine has shown that it has the potential to be a feasible alternative to methadone maintenance treatment. One potential benefit of buprenorphine compared with methadone that needs further investigation is a lower prevalence of medication interactions between buprenorphine and highly active antiretroviral treatment used to treat patients with HIV (Sullivan and Fiellin, 2005). Additional potential benefits of buprenorphine treatment are outlined in Figure 38.



**Figure 38 illustrates the potential benefits of buprenorphine.**

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## **Question 20: Can methadone and buprenorphine be abused?**

**Answer:** Both methadone and buprenorphine can be diverted from their intended recipients. This diversion occurs in countries that provide these medications via supervised dispensing (e.g., pharmacies) and by prescription. Oftentimes, this diversion is by individuals who are seeking a therapeutic benefit (e.g., unobserved treatment). Other times, this diversion results in abuse. The extent of these two types of diversion varies, although most studies note that the benefits of providing the treatment outweigh the risks associated with diversion. For instance, the efficacy of methadone has been demonstrated over the past 40 years (O'Connor and Fiellin, 2000). The provision of methadone and buprenorphine treatment was associated with a 75-percent decrease in fatal heroin overdoses in France (Lepere, Gourarier, Sanchez, et al., 2001; Auriacombe, Fatseas, Dubernet, et al., 2004).

In studies that have compared death rates from heroin overdose among those who are untreated and those who receive methadone, deaths are higher among untreated opioid-dependent individuals (Caplehorn, Dalton, Haldar, et al., 1996; Zanis and Woody, 1998).

### **Research Highlights**

#### ***Methadone Abuse***

Methadone can be diverted for oral or intravenous use (Fiellin and Lintzeris, 2003; Green, James, Gilbert, et al., 2000). Some diverted methadone can result in fatal overdoses; however, the rate of overdose among patients enrolled in methadone maintenance is low. A meta-analysis revealed a relative risk of death of 0.25 (95% CI: 0.19-0.33) for patients receiving methadone maintenance (Caplehorn et al., 1996). A study of nearly 10,000 individuals inducted onto methadone determined that the mortality rate was 7.1 deaths per 10,000 inductions (95% CI: 1.8± 12.4). In this same study, 51 percent of methadone-related deaths occurred in people who were not registered in methadone maintenance (Zador and Sunjic, 2002).

In addition, while methadone may be detected in drug-related deaths, it is often not the causative agent. In one study in the west of Scotland, during the period 1991–2001, methadone alone was judged to be the causative agent in only 29 percent (56) of drug-related deaths (Seymour, Black, Jay, et al., 2003).

Similarly, with the increased use of methadone as a treatment for chronic pain, the majority of methadone-related deaths in Australia and the United States are believed to be associated with the use of this medication for pain treatment instead of treatment of opioid dependence (Williamson, Foreman, White, et al., 1997; Center for Substance Abuse Treatment, 2004).

#### ***Buprenorphine Abuse***

As a partial agonist, buprenorphine has less potential for abuse than most full agonists. However, there is a reinforcing effect that subjects can experience with buprenorphine administration, especially via the injection route. This reinforcement is less likely if the subject has recently used a full agonist compound; in fact, buprenorphine can lead to a painful and uncomfortable precipitated withdrawal under this scenario. In addition, the development of a tablet that combines buprenorphine with naloxone, in a 4 to 1 ratio, has demonstrated decreased abuse potential and the ability to precipitate withdrawal in patients who are receiving a full opioid agonist (Mendelson, Jones, Welm, et al., 1999).

When the buprenorphine/naloxone combination tablet is taken sublingually, as prescribed, naloxone is poorly absorbed, and the patient receives a buprenorphine effect. However, if the tablet is dissolved and injected, the naloxone will antagonize the buprenorphine, resulting in a range of reactions, including blockade of opioid effects and precipitation of an immediate withdrawal. In this way, the combination gives the therapeutic benefit but greatly reduces opportunities for abuse by injection.

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### Short Communication

## The influence of distance on utilization of outpatient mental health aftercare following inpatient substance abuse treatment

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### Abstract

This study examined whether substance abuse patients who live farther from their source of outpatient mental health care were less likely to obtain aftercare following an inpatient treatment episode. For those patients who did receive aftercare, distance was evaluated as a predictor of the volume of care received. A national sample of 33,952 veterans discharged from Department of Veterans Affairs (VA) inpatient substance abuse treatment programs was analyzed using a two-part choice model utilizing logistic and linear regression. Patients living farther from their source of outpatient mental health care were less likely to obtain aftercare following inpatient substance abuse treatment. Patients who traveled 10 miles or less were 2.6 times more likely to obtain aftercare than those who traveled more than 50 miles. Only 40% of patients who lived more than 25 miles from the nearest aftercare facility obtained any aftercare services. Patients who received aftercare services had fewer visits if they lived farther from their source of aftercare. Lack of geographic access (distance) is a barrier to outpatient mental health care following inpatient substance abuse treatment, and influences the volume of care

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received once the decision to obtain aftercare is made. Aftercare services must be geographically accessible to ensure satisfactory utilization.

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## 1. Introduction

It is well established that utilization of outpatient mental health aftercare following episodes of acute inpatient substance abuse treatment results in better outcomes (Costello, 1980; Walker, Donovan, Kivlahan, & O'Leary, 1983). Active involvement in aftercare is also associated with reduced readmission rates (Moos & Moos, 1995; Peterson, Swindle, Phibbs, Recine, & Moos, 1994), even among patients with comorbid psychiatric disorders (Swindle, Phibbs, Paradise, Recine, & Moos, 1995).

Geographic access to care is an important determinant of health service use (Burgess & DeFiore, 1994; Mooney, Zwanziger, Phibbs, & Schmitt, 2000; White, 1986). Studies of hospital choice have shown consistently that increased distance reduces the probability that a hospital will be chosen by a patient for services (Holloway, Medendorp, & Bromberg, 1990; Luft et al., 1990; McGuirk & Porell, 1984). Because of the chronic nature of substance abuse disorders, proximity may be an especially important determinant of consistent outpatient treatment and, therefore, treatment success.

Although studies have evaluated the relationship between distance and utilization of certain types of outpatient care (Burgess & DeFiore, 1994; Fortney, Booth, Blow, & Bunn, 1995; Piette & Moos, 1996), we are aware of no studies that have specifically examined distance as a determinant of access to mental health aftercare for a broad range of substance abuse patients, or of the volume of services used.

The Department of Veterans Affairs (VA) provides a unique environment in which to study these issues. In fiscal year 1999 (FY99), VA medical centers (VAMCs) provided inpatient substance abuse treatment to 14,300 patients (Piette & Fong, 2000). In addition, VAMCs in FY99 provided more than 4.4 million outpatient mental health care visits to patients with substance abuse disorders. Thus, the sheer size of the VA health care system, nationwide service area, and detailed computerized medical records provide an unparalleled source of information on substance abuse patients' use of aftercare services. Because financial barriers are substantially reduced or eliminated for VA patients, nonfinancial barriers such as distance can be examined more clearly than in other health care systems. In addition, VA patients travel relatively far to reach their usual source of care (Burgess & DeFiore, 1994), thereby allowing examination of a greater range of the distance–service use relationship.

The goal of this study was to examine the role of distance in VA substance abuse patients' utilization of mental health aftercare. We examined whether patients who live farther from their source of VA outpatient mental health care were less likely to receive mental health services following inpatient substance abuse treatment. For patients who made the initial



choice to obtain aftercare, we evaluated the extent to which travel distance altered levels of aftercare utilization.

## 2. Methods

### 2.1. Data sources

The data for this study were obtained from clinical and administrative health service databases maintained by the VA. These databases include records of all inpatient and outpatient treatment delivered through VA facilities and reimbursable treatment delivered by non-VA providers. Additional data were obtained from the American Hospital Association (AHA) Annual Survey of Hospitals and the Area Resource File (ARF), compiled by the Office of Health Professions Analysis and the Research Bureau of Health Professions.

### 2.2. Patient selection

Our sample included patients admitted to substance abuse units of VA acute care hospitals in the continental United States (excluding Alaska) during FY93. VA inpatient substance abuse treatment has dropped precipitously in recent years (Piette & Fong, 2000). Thus, by using an earlier year rather than the most recent fiscal year, we were able to identify a larger sample. This strategy seemed reasonable since there is no reason to expect that the relationship between distance and service use would be affected by recent historical trends.

A total of 54,172 patients hospitalized for substance abuse treatment were identified. From this initial sample, we excluded patients who were discharged against medical advice, were rehospitalized or died within 90 days of the index discharge, or did not have a valid zip code of residence. The resulting analytic sample included a total of 33,952 patients who received inpatient substance abuse treatment and were eligible for outpatient aftercare.

### 2.3. Variable definition

Using inpatient records, we obtained patients' sociodemographic characteristics, psychiatric comorbidities, and the specific substance(s) used by the patient (Table 1).

To control for nonpsychiatric medical comorbidities that could influence aftercare attendance, we used the Charlson comorbidity index (Charlson, Pompei, Ales, & MacKenzie, 1987) as modified by Deyo, Cherkin, and Ciol (1992) for use with ICD-9 codes. We calculated patients' medical comorbidity scores using diagnoses recorded during the index episode and all other inpatient admissions in the prior 12 months. We used the distance from the patient's residence to the *nearest* VA facility offering aftercare services, rather than distance to an outpatient clinic in which services were actually received, to measure geographic access to aftercare. This choice was made to ensure that measurement was consistent for patients who did and did not receive aftercare. Distance was defined as the straight-line distance from the center of the patient's five-digit zip code to the center of the

Table 1

Sociodemographic and clinical characteristics of 33,952 VA patients receiving inpatient substance abuse treatment during fiscal year 1993

	<i>N</i>	Percent or mean $\pm$ S.D.
<i>Geographic access (distance to nearest outpatient facility)</i>		
10 miles or less	19,709	58.1
11–25 miles	5903	17.4
26–50 miles	4658	13.7
Greater than 50 miles	3682	10.8
<i>Patient demographics</i>		
Used aftercare within 90 days	19,034	56.1
Age		42.6 $\pm$ 10
Male	33,409	98.4
Black	13,508	39.8
White	18,274	53.8
Other race	2170	6.4
Married	7181	21.2
Service connected eligibility	8904	26.2
<i>Substance abuse diagnoses</i>		
Alcohol only	13,072	38.5
Drug only	4033	11.9
Alcohol and drug	16,847	49.6
<i>Psychiatric comorbidities</i>		
One or more psychiatric comorbidities	22,989	67.7
Bipolar depression	812	2.4
Unipolar depression	3242	9.5
PTSD	5428	16.0
Schizophrenia	861	2.5
Antisocial personality disorder	1208	3.6
<i>One or more prior hospitalizations</i>		
	6016	17.7
<i>Comorbid medical diagnoses<sup>a</sup></i>		
Charlson index = 0	29,824	87.8
Mean Charlson index for remainder	4128	1.33 $\pm$ 0.9
<i>Hospital characteristics</i>		
Teaching	19,615	57.8
Medical school affiliate	25,734	75.8
<i>County level demographics</i>		
Population density		3498.2 $\pm$ 8516
Percent non-white collar		27.5 $\pm$ 17
Percent white collar workers		55.4 $\pm$ 7
Percent high school graduates		75.8 $\pm$ 7
Unemployment rate		7.2 $\pm$ 2

<sup>a</sup> The Charlson index ranges from 0 to 4+. Higher scores indicate greater comorbidity.

Table 2

Logistic regression estimates of the effects of distance and individual, hospital and regional characteristics on the probability of receiving aftercare

	Adjusted odds ratio	95% confidence interval
<i>Geographic access<sup>a</sup></i>		
Distance (up to 10 miles)	2.56***	2.32–2.81
Distance (11–25 miles)	1.91***	1.72–2.13
Distance (26–50 miles)	1.21***	1.08–1.35
<i>Patient demographics</i>		
Age (5-year increments)	0.95***	0.93–0.96
Married	1.23***	1.16–1.32
Service connected eligibility	1.12**	1.04–1.18
<i>Clinical characteristics</i>		
Marijuana use disorder	1.14**	1.06–1.23
Amphetamine use disorder	1.27**	1.07–1.50
Bipolar depression	1.46**	1.20–1.79
Unipolar depression	1.20**	1.07–1.34
PTSD	1.56***	1.37–1.78
Schizophrenia	1.44***	1.19–1.75
Antisocial personality disorder	0.81**	0.69–0.94
Number of psychiatric diagnoses	1.15***	1.09–1.22
<i>Medical comorbidity index</i>		
1	0.81***	0.74–0.89
2	0.66***	0.51–0.84
3	0.69	0.47–1.01
4	0.77	0.47–1.23
>4	0.51*	0.23–1.12
<i>Hospital characteristics</i>		
Teaching	1.18***	1.10–1.26
Medical school affiliate	0.95	0.88–1.02
<i>County-level demographics</i>		
Percent non-white collar	1.16	0.91–1.48
Percent white collar	0.15***	0.09–0.25
Percent high school graduates	12.97***	6.52–25.80
Unemployment rate	0.03**	0.00–0.16

Initial likelihood = 46,567.25. Reduction in likelihood = 13,539.41.  $df = 33$ ,  $P < .0001$ .

<sup>a</sup> Reference group for distance: patients who traveled more than 50 miles.

\*  $P < .05$ .

\*\*  $P < .01$ .

\*\*\*  $P < .001$ .

Table 3

Multiple linear regression analysis predicting number of outpatient aftercare visits for 19,034 veterans beginning aftercare within 90 days of discharge

	Unstandardized coefficient	t  (df= 1)
<i>Geographic access<sup>a</sup></i>		
Distance (up to 10 miles)	2.80***	3.82
Distance (11–25 miles)	0.67	0.99
Distance (26–50 miles)	0.02	0.04
<i>Patient demographics</i>		
Age (5-year increments)	0.04**	3.08
Black	– 0.51*	2.24
Hispanic	1.03*	1.99
Other race	– 1.03	1.87
Married	– 1.20***	5.27
Service connected eligibility	– 1.05***	4.93
<i>Clinical characteristics</i>		
Drug use disorder	3.14***	9.45
Alcohol and drug use disorder	0.93***	4.16
Amphetamine use disorder	1.68**	2.99
Other drug use disorder	– 1.75**	2.78
Bipolar depression	– 1.53**	2.92
PTSD	0.70*	2.02
Antisocial personality disorder	– 1.68**	3.46
Other personality disorder	– 1.45**	4.48
Other psychiatric disorder	– 1.09*	2.22
Prior hospitalization	0.33	1.40
Other outpatient treatment	8.88***	47.35
<i>Medical comorbidity index</i>		
1	– 0.67*	2.06
2	– 2.35*	2.62
3	– 1.66	1.25
4	0.14	0.08
>4	2.63	0.78
<i>Hospital characteristics</i>		
Teaching	1.50***	6.10
Medical school affiliate	– 1.75***	6.43
<i>County-level demographics</i>		
Percent non-white	5.89***	6.87
Percent white collar	– 18.45***	9.34
Percent high school graduates	26.25***	10.72
Unemployment rate	18.37*	2.83

nearest outpatient facility's five-digit zip code (Garnick, Luft, & Robinson, 1987). While travel time is what actually influences service use, straight-line distance is a robust proxy for travel time in studies of geographic access to health care (Phibbs & Luft, 1995).

#### 2.4. Definition of dependent variables and statistical analyses

Factors that influence patients' initial choice to seek specific health services may be different than the factors that influence the amount of care sought by the patient once the initial choice to obtain care is made. Thus, we used a two-part choice model to examine the use of mental health aftercare. These models have been used in previous research to study outpatient health care choices (Burgess & DeFiore, 1994) and, perhaps most significantly, as part of the Rand Health Insurance Experiment, which examined both outpatient and inpatient services (Duan, Manning, & Morris, 1983; Manning et al., 1987).

##### 2.4.1. Use of any outpatient aftercare (yes/no)

Using outpatient records, we constructed a variable indicating whether each patient received aftercare in a VA substance abuse, psychiatric, or other mental health clinic in the 90 days following the index discharge. Our interest was in the use of aftercare in the immediate postdischarge period since aftercare attendance during this period is an important protective factor against rehospitalization (Costello, 1980; Walker et al., 1983).

Logistic regression was used to evaluate the influence of geographic access on the likelihood of having any mental health aftercare within 90 days postdischarge controlling for the potential confounding effects of patient and facility characteristics.

##### 2.4.2. Volume of aftercare use among patients with at least one visit

For patients who received some aftercare within 90 days of discharge, the number of mental health clinic visits was calculated. An ordinary least squares (OLS) multiple linear regression analysis was performed to evaluate the influence of distance, controlling for covariates.

### 3. Results

#### 3.1. Aftercare attendance

After controlling for statistically significant covariates, distance to outpatient treatment was an important predictor of aftercare attendance (Table 2). Patients who traveled 10 miles or less

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Notes to Table 3:

$R^2=.14$ ,  $F=92.33$ ,  $df=34$ ,  $P<.0001$ . Mean number of visits = 11.7, S.D. = 14.2. OLS was determined to be an appropriate analysis after examination of the distribution of number of visits. A count data model was not required.

<sup>a</sup> Reference group for distance: patients who traveled more than 50 miles.

\*  $P<.05$ .

\*\*  $P<.01$ .

\*\*\*  $P<.001$ .

were 2.6 times more likely to attend aftercare than those who traveled more than 50 miles ( $OR = 2.56$ , 95%  $CI = 2.32, 2.81$ ). For those who traveled between 11 and 25 miles, the odds of attending aftercare were reduced by 65% ( $OR = 1.91$ , 95%  $CI = 1.72, 2.13$ ). Based on the resulting model, the probability of attending aftercare for a representative patient (a 43-year-old married Caucasian male treated for alcohol abuse with no prior inpatient treatment and no comorbid psychiatric or medical conditions) falls to less than 50% when the patient must travel more than 25 miles to receive care.

Aside from the adjusted distance effect estimates, other important predictors of aftercare use (such as community education level) also are evident from the model shown in [Table 2](#).

### 3.2. Volume of aftercare use

[Table 3](#) shows that once the initial choice to seek aftercare was made, patients who lived farther from the nearest outpatient facility attended fewer aftercare sessions. Patients who traveled 10 miles or less received 2.8 more aftercare sessions ( $t = 3.82$ ,  $P < .0001$ ) than patients who traveled more than 50 miles.

## 4. Discussion

To our knowledge, this study is the first to estimate the impact of distance to outpatient mental health care on aftercare attendance following inpatient substance abuse treatment. Our results demonstrate that there is a rapid decline in the probability of obtaining aftercare as distance increases. This effect remains robust even after controlling for factors that are known to influence receipt of outpatient aftercare, such as psychiatric and medical comorbidities, age, and community demographics.

These results are particularly compelling in a study of VA patients since they incur no out-of-pocket costs for their care. Thus, we implicitly controlled for other common barriers to health care access such as the extent to which outpatient mental health services are covered by a patient's insurance benefits. Nevertheless, the degree to which our findings can be generalized to other populations may be limited by the fact that our study was restricted to a group of predominately male veterans.

The initial choice to seek mental health aftercare was predicted by different factors than the volume of aftercare received once the decision to seek care was made. However, volume of aftercare use was also influenced by distance. The effect of distance on the volume of aftercare use tapered off at distances exceeding 10 miles, which may reflect the fact that those who live farther away (i.e., in rural areas) may be slightly more willing to travel greater distances because the time to travel a mile in rural areas is less.

In contrast with the initial choice to seek aftercare, the volume of aftercare use appears to be influenced by patients' race, and type of substance abuse. Although the focus of this study was distance, the differences between characteristics that influence the choice to seek care versus the volume of care received are not fully understood and suggest the need for further research.

With ongoing emphasis on health care reform and cost reduction, our findings suggest that attention should be paid to geographic access. If greater aftercare utilization is a priority in seeking to reduce readmissions and recidivism, aftercare services may need to be located closer to the homes of patients. In addition, geographic access is an issue of increasing importance as more and more inpatient care is shifted to high intensity outpatient care.

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# Use of a 'microecological technique' to study crime incidents around methadone maintenance treatment centers

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## ABSTRACT

**Aims** Concern about crime is a significant barrier to the establishment of methadone treatment centers (MTCs). Methadone maintenance reduces crime among those treated, but the relationship between MTCs and neighborhood crime is unknown. We evaluated crime around MTCs. **Setting** Baltimore City, MD, USA. **Participants** We evaluated crime around 13 MTCs and three types of control locations: 13 convenience stores (stores), 13 residential points and 10 general medical hospitals. **Measures** We collected reports of Part 1 crimes from 1 January 1999 to 31 December 2001 from the Baltimore City Police Department. **Design** Crimes and residential point locations were mapped electronically by street address (geocoded), and MTCs, hospitals and stores were mapped by visiting the sites with a global positioning satellite (GPS) locator. Concentric circular 'buffers' were drawn at 25-m intervals up to 300 m around each site. We used Poisson regression to assess the relationship between crime counts (incidents per unit area) and distance from the site. **Findings** There was no significant geographic relationship between crime counts and MTCs or hospitals. A significant negative relationship (parameter estimate  $-0.3127$ ,  $P < 0.04$ ) existed around stores in the daytime (7 am–7 pm), indicating higher crime counts closer to the stores. We found a significant positive relationship around residential points during daytime ( $0.5180$ ,  $P < 0.0001$ ) and at night ( $0.3303$ ,  $P < 0.0001$ ), indicating higher crime counts further away. **Conclusions** Methadone treatment centers, in contrast to convenience stores, are not associated geographically with crime.

**Keywords** Crime, geocoding, methadone maintenance, neighborhood, spatial analysis.

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## INTRODUCTION

The aim of this study is to determine whether there is a geographic relationship between methadone treatment centers (MTCs) and neighborhood crime. Methadone maintenance is well established as an effective treatment for opiate dependence [1–3]. Opioid dependence is a global public health problem, with an estimated 24–32 million opioid users (12–14 million heroin users) worldwide in 2009, including 3.1–3.5 million users in Europe [4]. Nevertheless, access to treatment is limited in many communities that oppose the establishment of new methadone maintenance treatment centers (MTCs), due

largely to concerns about crime [5,6]. This resistance exists despite extensive research over several decades, showing that methadone maintenance treatment decreases crime among treated patients. For example, a study of 1075 heroin users found that methadone maintenance plus psychosocial treatment decreased crime, resulting in decreased societal costs [7].

Community concerns about MTCs causing crime reflect a difference between 'clinical' and 'ecological' perspectives. While the clinical perspective has established that successfully treated patients commit fewer crimes [8], there is no empirical evidence on the ecological relationship between MTCs and neighborhood crime. Three

possible relationships could exist, and plausible theories support each relationship. MTCs could decrease neighborhood crime by treating opiate users who live nearby, thereby decreasing their risk of criminal behavior. MTCs could increase crime if they attract untreated or partially treated users into the neighborhood, thereby increasing the local density of people likely to commit crimes [9]. Finally, MTCs could have no crime impact if neighborhood crime relates largely to other factors.

This study addresses the debate by evaluating relevant empirical data with a technique that has not been applied previously to this issue. Previous studies of the geographic (spatial) relationship between locations of substance availability (e.g. alcohol outlets, location of illegal drug possession and sales) and crime have used relationships between locations and crime rates averaged over large areas, typically postal codes or census tracts [9–11]. This study is the first of which we are aware to use a more fine-grained ‘microecological’ approach. Instead of studying a population of patients or a large geographic area where the MTCs are located, we evaluated crime rates in terms of increasing spatial distance *within* individual MTC neighborhoods.

The study was conducted in Baltimore, MD, USA, an urban environment with a high rate of heroin use [12, 13] and high crime rate [14]. The city had 16 methadone treatment centers (MTCs) in operation during the study period. A comparison of crime before and after the establishment of MTCs was not possible, because most of the MTCs in Baltimore had been in operation before the advent of geocodable electronic crime data.

## METHODS

Details of the ‘microecologic technique’ have been published previously [15]. In brief, we obtained a database listing all Federal Bureau of Investigation (FBI) Uniform Crime Report ‘Part 1’ crimes [homicide, sexual assault, robbery, aggravated assault, burglary, larceny (including theft from a motor vehicle), auto theft and arson] [16] in Baltimore City, MD, from 1 January 1999 to 31 December 2001 from the Baltimore City Police Department. We identified 16 MTCs operating in Baltimore during this study period. One was excluded because it was located on the sixth floor of a general medical hospital, making it impossible to differentiate its crimes from those associated with the hospital. Three of the remaining MTCs were analyzed as one clinic, because their front entrances were within 25 m of each other, making it impossible to analyze their crime data separately. Thus, we included data from 13 MTCs whose characteristics we obtained by telephone survey (Table 1). Of these, eight were on the campus of or near a hospital, but not in the same building as the hospital. Four MTCs offered buprenorphine for

**Table 1** Characteristics of 13<sup>a</sup> Baltimore City, Maryland methadone maintenance treatment centers (MTCs) operating 1 January 1999 to 31 December 2001.

	<i>Min</i>	<i>Max</i>	<i>Mode</i>	
Opening time	5:30 am	11 am	7 am	
Closing time	4 pm	7:30 pm	6 pm	
	<i>Min</i>	<i>Max</i>	<i>Mean</i>	<i>Median</i>
Daily patient census	55	600	298	300

<sup>a</sup>Includes combined data from three MTCs whose entrances were within 25 m of another MTC (see text).

opioid detoxification or maintenance therapy, in addition to methadone.

To help assess the significance of any relationship between MTCs and crime, we evaluated crime around three types of control sites in Baltimore City, MD. MTCs might have more crime than adjacent locations because of having higher foot traffic. High foot-traffic areas (areas with higher density of people) may have more crime than low foot-traffic areas because offenders are more likely to meet victims/targets in such areas [17]. Therefore, we selected two ‘high foot-traffic’ sites (general hospitals and convenience stores) and one ‘low foot-traffic’ site (residential points) as controls. General medical hospitals (10 in operation in Baltimore during the study period) were chosen because they, like MTCs, provide medical care. ‘Convenience stores’ were those defined as such on the Switchboard.com [18] website. Residential points were defined as addresses in the middle of a block on a small secondary street within a geographic area identified as ‘residential’ by local zoning maps.

Thirteen convenience stores and 13 residential sites were matched to the 13 MTCs based on 20 relevant census and crime variables (Table 2), which previous factor analytical research has shown can identify neighborhoods with high rates of violent crime [19]. These variables were entered into a factor analysis by Baltimore City Census Block Group (CBG); the analysis was pre-defined to generate a single factor score. Control sites were chosen for each clinic so that the factor scores of their CBGs were closest to the factor score of their matched clinic. Hospitals could not be matched to the MTCs due to the limited number of hospitals (10) available for matching.

## Data and geocoding

Crime locations and residential control sites were mapped electronically by ‘geocoding’ their street addresses using the ArcGIS 9 computer program [20]. Geocoding is a computerized process in which a street address is con-

**Table 2** Variables used in the factor analysis for matching census block groups of methadone maintenance treatment centers (MTCs) and control study sites.

Census variables
% Staying at the same house for more than 5 years
Population per square mile
Household size
% Female-headed households
% People with no high school diploma
Per capita income
Median household income
Percent with income below poverty level
% Service workers
% People unemployed
% Households with public assistance income
% Households with no worker
% Non-white
'Racial heterogeneity' (count of different races reported)
% Vacant houses
% Households renting home
Median gross rent
Median value of owner-occupied home
Crime variables
Total crimes in 2000
Total drug-related crimes

verted into a map location (latitude and longitude) [21]. The locations of MTCs, convenience stores and hospitals were determined by visiting the sites and reading the latitude and longitude on a global positioning satellite (GPS) locator. Site visits were necessary in these cases, because street addresses of non-residential sites are sometimes not precise enough to generate an accurate latitude and longitude. For example, convenience stores are sometimes located in large parking lots or malls, along with other stores. In order to maintain the privacy of people living at the residential sites, the locations of the residential sites were found by geocoding, rather than by visiting the site.

#### 'Buffering' sites and counting crimes

We used a 'buffer' methodology to determine the geographic relationship between study sites and neighborhood crime. Concentric circular, non-overlapping, doughnut-shaped buffers were defined at 25-m intervals for up to 300-m radius around each study site. Crimes were counted within each buffer. In order to compare crime quantitatively across buffers of increasing size, the number of crimes was corrected for the area of each buffer to generate crime counts per unit area ('crime counts'). To avoid crime counts <1, the 'unit area' was defined as 1962.5 m<sup>2</sup> [the size of the smallest (25-m) buffer]. Similar buffer methodologies have been used to study crime around housing projects [22] and supportive housing [23].

#### Statistical analysis

Poisson regression analyses were used to evaluate the relationship between crime counts and distance from a site. First, a generalized additive model (GAM) with a spline term was used to fit a line to scatter-plots to visualize the data. The GAM graphs indicated that most of the variation in crime incidents was within the first 100 m (first four buffers) of the sites (data not shown). Thus, further data analysis included only crime incidents within 100 m of the study sites. Further analyses used a Poisson distribution and generalized linear model to analyze crime counts around the study sites, generating a parameter estimate ( $\beta$ ) through a least-squares analysis. A significant positive  $\beta$  ('positive crime slope') indicates a higher crime rate with increasing distance from the study site, while a significant negative  $\beta$  ('negative crime slope') indicates a higher crime rate closer to the study site. All analyses were performed with SAS version 9.1 [24].

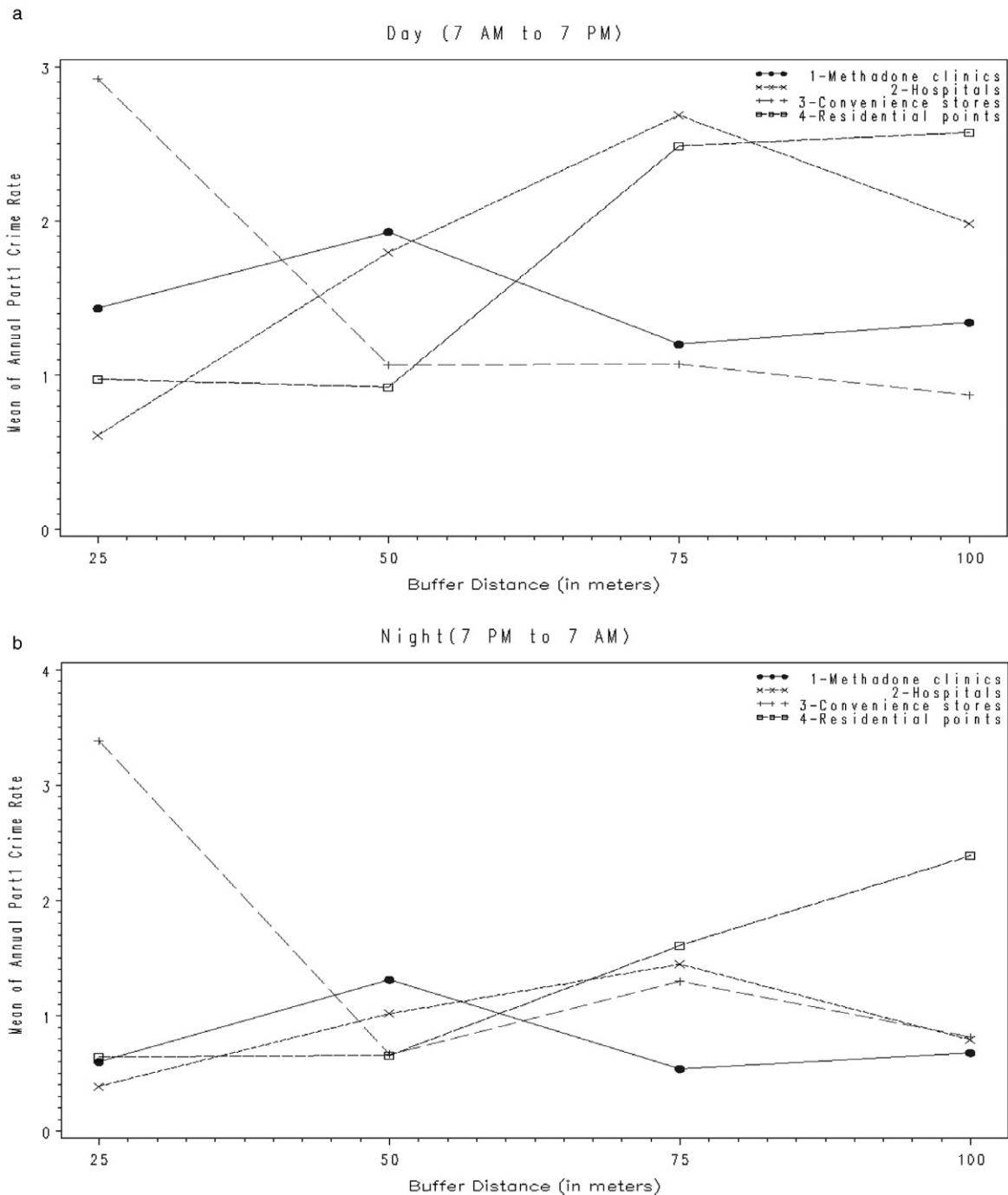
'Within-group' comparisons to evaluate the relationship between crime counts and distance from the site (crime slopes) were performed separately for MTCs, convenience stores, hospitals and residential points. Because crimes can occur at night, when MTCs are closed, we controlled for time of day by analyzing separately crimes occurring during the day (7 a.m.–7 p.m.), the hours when most MTCs are open (Table 1), and at night (7 p.m.–7 a.m.).

#### RESULTS

There was no significant change in crime counts with increasing distance from MTCs or hospitals (Fig. 1), as indicated by non-significant values for parameter estimates of crime slopes (Table 3). In contrast, there was a significant decrease in crime counts with increasing distance from convenience stores during both daytime and night-time (Fig. 1, Table 3, daytime parameter estimate  $-0.3127$ ,  $P < 0.04$ , night time parameter estimate  $-0.3235$ ,  $P < 0.0623$ ). Around residential sites, there was a significant increase in crime counts, with increasing distance from the site during both daytime ( $0.5180$ ,  $P < 0.0001$ ) and night-time ( $0.3303$ ,  $P < 0.0001$ ).

#### DISCUSSION

This study found no significant change in crime counts with increasing distance (up to 100 m) from MTCs, suggesting that MTCs are not a geographic focus for crime. In contrast, there was a significant decline in crime counts with increasing distance from convenience stores and a significant increase in crime counts with increasing



**Figure 1** Crime rates around methadone maintenance treatment clinics, general medical hospitals, convenience stores and residential points in Baltimore City, MD (1999–2001). Crimes were all Federal Bureau of Investigation (FBI) Part I crimes [homicide, sexual assault, robbery, aggravated assault, burglary, larceny (including theft from a motor vehicle), auto theft, and arson] reported in Baltimore City, MD between 1 January 1999 and 31 December 2001. Crime rate—crimes per 'unit area' (1962 m<sup>2</sup>, the area of a 25-m circle/buffer). Buffer distance—radius of circular/doughnut-shaped areas defined around study sites. Study sites were 13 methadone maintenance treatment centers (MTCs), 10 general medical hospitals, 13 convenience stores and 13 residential points (residential addresses in the middle of the block on secondary streets). Convenience stores were matched to the MTCs by neighborhood characteristics (see text for details). Mapping of locations was based on street address for crime locations and residential sites and global positioning satellite (GPS) for other sites. (a) Crimes between 7 a.m. and 7 p.m., when MTCs are open. (b) Crimes between 7 p.m. and 7 a.m., when MTCs are closed

**Table 3** Poisson regression analysis of the relationship between crime counts<sup>a</sup> and distance ( $\leq 100$  m) from study site.

Type of site	Time of day	Parameter estimate <sup>b</sup>	Standard error	Lower confidence limit	Upper confidence limit	Z	P value
MTC <sup>c</sup> [13]	Day <sup>d</sup>	-0.0938	0.2243	-0.5334	0.3457	-0.42	0.6757
	Night <sup>e</sup>	-0.1614	0.2167	-0.5862	0.2634	-0.74	0.4564
Convenience Store [13]	Day	-0.3127	0.1553	-0.6171	-0.0083	-2.01	0.0441
	Night	-0.3235	0.1735	-0.6635	0.0166	-1.86	0.0623
Residential Site [13]	Day	0.3303	0.0511	0.2302	0.4304	6.47	<.0001
	Night	0.518	0.0947	0.3325	0.7035	5.47	<.0001
General medical hospital [10]	Day	0.086	0.1353	-0.1792	0.3511	0.64	0.5251
	Night	-0.056	0.1533	-0.3564	0.2443	-0.37	0.7146

<sup>a</sup>Crime count: number of crime incidents per area in each concentric ring at 25-m intervals around the site. <sup>b</sup>Parameter estimate: estimated 'crime slope' relating crime counts with distance from study site. Positive parameter estimate indicates increasing crime counts with increasing distance from the site. Negative parameter estimate indicates decreasing crime counts with increasing distance from the site. <sup>c</sup>MTC: methadone maintenance treatment center.

<sup>d</sup>Day: 7 a.m.–7 p.m. <sup>e</sup>Night: 7 p.m.–7 a.m. Italics indicate significant results.

distance from the residential sites, indicating that the microecological technique is capable of detecting places that are or are not geographic foci of crime. The observed crime pattern around convenience stores (high foot-traffic areas) and around residential sites (low foot-traffic areas in the middle of small residential blocks) is consistent with the previously shown positive correlation between crime and increased density of people at a site [17]. Overall, the pattern of findings supports the validity and sensitivity of our microecological technique, and strengthens confidence in our primary finding of no significant increase in crime counts closer to MTCs.

An estimated 282 000 Americans were dependent on or abusing heroin and another 1.72 million were dependent on or abusing prescription pain relievers in 2008 [25]. In contrast, only about 265 000 patients were receiving opiate agonist treatment in 1108 US treatment facilities [26]. The European Union had more than 1 million regular opioid users in 2006, but only 25 000 patients receiving methadone maintenance treatment [27]. Thus, there is a public health need for more MTCs to treat the large numbers of people addicted to opiates. Our finding that MTCs are not associated with increases in neighborhood crime addresses a major impediment to the establishment of new clinics, and should lead to greater availability of methadone maintenance treatment for the many people who need it.

This study has several strengths, including the use of a microecological technique that evaluates geographic neighborhoods rather than patient populations, use of control sites matched to the MTCs to minimize confounding by degree of foot traffic and other neighborhood characteristics known to influence crime rates, and the inclusion of data from all but one of the MTCs operating in Baltimore City during the study period.

This study has several limitations. First, the data show substantial variability, as reflected in large confidence

intervals. For example, although methadone clinics and residential points have different crime slopes (different sign for the parameter estimate), there is no significant interaction term between the two groups when they are compared in a between-groups comparison. Secondly, this study has uncertain external validity because it involved a relatively small number [15] of MTCs in a single city. However, there is no obvious manner in which Baltimore City MTCs differ from those in other areas of the United States or abroad, nor is there any reason that the neighborhood factors influencing crime in Baltimore should differ from those elsewhere. Indeed, Baltimore may be an 'ideal' setting for this type of study, given its high rate of heroin use (Baltimore has been called the 'heroin capital' of the United States [12,13]), urban environment and high crime rate [14].

The stigma against methadone maintenance treatment, including concerns about crime, exists throughout the world [28–31], regardless of whether methadone is dispensed in centralized methadone treatment centers or by prescription through community pharmacies. For example, a survey of pharmacists in England found that many expressed concern about shoplifting and aggression if they were to begin to dispense methadone [32]. Residents both in the United Kingdom and Canada voice fears that methadone treatment centers may increase crime, resulting in difficulty opening or keeping open methadone clinics [33–35]. This study provides strong evidence against a major reason for the social stigma concerning methadone maintenance, i.e. concerns about crime. A major issue in the NIMBY ('not in my back yard') phenomenon for MTCs is the need for patients to come in daily for dosing. Buprenorphine, an opioid partial agonist now used in many countries for opioid substitution, can be prescribed by physicians and dispensed for home administration. Because there is no need for patients to come to a specialized clinic for regular dosing, the hope is



that buprenorphine treatment will be less stigmatized and better accepted than methadone treatment.

Finally, a key conceptual issue for any study involving crime is how to quantify crime. Three major parameters have been used to measure crime in social science studies, each with its own advantages and disadvantages: crime incidents (used in this study), arrests and 911 calls. Crime incidents, being generated from complaints of crime, are not subject to policy changes in police enforcement, unlike arrest data. However, incident data have the disadvantage of not recording 'victimless' crimes, such as many drug crimes. Databases of 911 calls have the disadvantage of containing a large number of 'unfounded' events; that is, when the police arrive at the scene of the call, there is no evidence of the reported crime. However, 911 databases may be a more sensitive measure of community concerns about crime.

Overall, our data show that MTCs are not a geographic focus of crime, thus providing both strong evidence to alleviate neighborhood concerns about the establishment and operation of MTCs and quantitative information to combat the stigma of methadone substitution treatment. As more MTCs open and more geocodable crime data become available, future research can attempt to confirm and expand our findings using before-and-after designs and different types of crime data.

## CONCLUSION

This study found no significant increase in crime around MTCs, while finding the expected significant increase around convenience stores, which also have high foot traffic. These results do not support the common neighborhood concern of MTCs as geographic foci of crime, and may ease the establishment of new MTCs. Studies using the microecological technique may inform more clearly the social and political debate around the siting of MTCs.

## Declarations of interest

SB is Medical Director of the Baltimore Veterans Affairs Medical Center Opiate Agonist Treatment Program. Otherwise, the authors have no conflicts of interest in relation to this study or connection with the tobacco, alcohol, pharmaceutical or gaming industries. There are no contractual constraints on publishing this study.

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# METHADONE MAINTENANCE TREATMENT

*Methadone maintenance treatment (MMT) can help injection drug users (IDUs) reduce or stop injecting and return to productive lives. However, its use is still sometimes publicly controversial and many factors limit the effectiveness of MMT services. New federal regulations, which have overhauled the MMT system, promise a more flexible approach and improved delivery of these needed, life-saving services.*

## Opiate Addiction Is a Major Individual and Public Health Problem

It is estimated that at least 980,000 people in the United States are currently addicted to heroin and other opiates (such as oxycontin, dilaudid, and hydrocone). They risk premature death and often suffer from HIV, hepatitis B or C, sexually transmitted disease (STDs), liver disease from alcohol abuse, and other physical and mental health problems. It is estimated that 5,000-10,000 IDUs die of drug overdoses every year. Many are involved with the criminal justice system.

A 1997 National Institutes of Health (NIH) report estimated the financial costs of untreated opiate addiction at \$20 billion per year. These costs, combined with the social costs of destroyed families, destabilized communities, increased crime, increased disease transmission, and increased health care costs, mean that opiate addiction is a major problem for affected individuals and society.

## Methadone Maintenance Treatment Is the Most Effective Treatment for Opiate Addiction

Methadone is a synthetic agent that works by "occupying" the brain recep-

tor sites affected by heroin and other opiates. Methadone:

- blocks the euphoric and sedating effects of opiates;
- relieves the craving for opiates that is a major factor in relapse;
- relieves symptoms associated with withdrawal from opiates;
- does not cause euphoria or intoxication itself (with stable dosing), thus allowing a person to work and participate normally in society;
- is excreted slowly so it can be taken only once a day.

Methadone maintenance treatment, a program in which addicted individuals receive daily doses of methadone, was initially developed during the 1960s as part of a broad, multicomponent treatment program that also emphasized resocialization and vocational training.

*Methadone maintenance treatment has important benefits for addicted individuals and for society.*

These benefits include:

- reduced or stopped use of injection drugs;
- reduced risk of overdose and of acquiring or transmitting diseases

such as HIV, hepatitis B or C, bacterial infections, endocarditis, soft tissue infections, thrombophlebitis, tuberculosis, and STDs;

- reduced mortality – the median death rate of opiate-dependent individuals in MMT is 30 percent of the rate of those not in MMT;
- possible reduction in sexual risk behaviors, although evidence on this point is conflicting;
- reduced criminal activity;
- improved family stability and employment potential; and
- improved pregnancy outcomes.

Using commonly accepted criteria for medical interventions, several studies have also shown that MMT is extremely cost-effective.

## Key Issues in Effective Methadone Maintenance Treatment

### Dose

Most patients require a dose of 60-120 mg/day to achieve optimum therapeutic effects of methadone. Compared to those on lower doses, patients on higher doses are shown to stay in treatment



longer, use less heroin and other drugs, and have lower incidence of HIV infection. Some patients need even higher doses for fully effective treatment.

Studies of methadone effectiveness have shown a dose-response relationship, with higher doses more effective in reducing heroin use, helping patients stay in treatment, and reducing criminal activity. Despite compelling evidence that doses need to be determined on an individual basis, that higher doses are more effective, and that doses of 60-120 mg/day are required for most patients, some clinics administer fixed doses to all patients and provide less than optimal doses.

#### *Length of treatment*

Studies have shown that good outcomes from substance abuse treatment are unequivocally contingent on adequate length of treatment. A research-based guide on the principles of substance abuse treatment, released in 1999 by the National Institute on Drug Abuse (NIDA), notes that "For methadone maintenance, 12 months of treatment is the minimum, and some opiate-addicted individuals will continue to benefit from methadone maintenance treatment over a period of years." Despite this fact, the majority of MMT patients leave before 1 year, either because they drop out, the clinic encourages them to leave, or they are discharged for not complying with program regulations. Most of those who discontinue MMT later relapse to heroin use. This illustrates the difficulty of the addiction recovery process and the fact that individuals may need multiple episodes of treatment over time.

#### *The need to tailor treatment to subgroups of IDUs and to individual patients*

IDUs come to MMT with a broad range of issues and problems in addition to their drug addiction. For example, about 40 percent of patients entering methadone treatment use cocaine or crack as well as heroin; perhaps a

quarter also abuse alcohol. Studies have shown that 67-84% of MMT patients have been infected with hepatitis C. About 10 million people in the U.S. have co-occurring substance abuse and mental disorders; more than 40 percent of those with addictive disorders also have mental disorders. IDUs frequently have unstable living situations and may need multiple social services. Treatment programs tailored to the specific needs of patients can respond more effectively to these varied types of patients.

#### *Continued use of heroin, cocaine, alcohol, and other drugs*

It is relatively common for MMT patients to continue using heroin, other drugs such as cocaine or marijuana, and alcohol after admission to treatment. This reflects the long history of use, the complexity of patients' situations and reasons for using drugs, and the biological basis of addiction. Many patients in treatment do not have complete control over their addictions at all times. Realistic expectations of treatment reflect the understanding that recovery is a day-to-day process with occasional relapses.

### **The Regulation and Administration of MMT has Undergone a Radical Change**

#### *The context for change*

Despite 30 years of experience and widespread acceptance by addiction specialists and health agencies, MMT has sometimes been publicly controversial in the U.S. and other countries. Critics have cited the belief that methadone treatment merely substitutes one addiction for another and that achieving a drug-free state is the only valid treatment goal. Misunderstandings about the nature of drug addiction (not seeing it as a biomedical condition) are part of the reason why MMT has sometimes been met with limited acceptance by communities, health care providers, and the public. Critics opposed to expanding

MMT programs also express concerns that they may be a magnet for crime and drug dealing and that patients will divert methadone (sell it to supplement their income or buy or sell it to help friends in withdrawal). As a result, the use of methadone to treat addiction has been heavily regulated and strictly controlled in this country. For example, until now, MMT has been delivered only through specially licensed clinics, called Opioid Treatment Programs.

These regulations and controls have meant that MMT programs have had limited flexibility and ability to respond to the needs of patients, including in such key areas as dose and length of treatment. The regulations also have limited the number of physicians who are available to treat heroin addiction and the settings and locations in which treatment can occur.

#### *The change*

In May 2001, the U.S. Department of Health and Human Services (DHHS) announced a new system for regulating and monitoring MMT. Under this new system, oversight responsibility for MMT in the United States shifted from the Food and Drug Administration (FDA) to the Substance Abuse and Mental Health Services Administration's Center for Substance Abuse Treatment (CSAT).

This new system represents a fundamental change in the approach to substance abuse treatment and in the federal government's role in ensuring effective and accountable MMT programs. It relies on accreditation of MMT programs by independent organizations and states, in accordance with treatment standards that have been developed by CSAT over the last 10 years.

These standards reflect current knowledge about the nature of opiate addiction as a chronic brain disease and the principles underlying effective long-term, comprehensive treatment. The standards are based on "best practice guidelines" and

emphasize improving quality of care in areas such as individualized treatment planning, increased medical supervision, and assessment of patients. The new system continues to accommodate community concerns, however, by retaining regulations that are designed to reduce diversion of methadone.

The designers of this new approach believe that shifting to an accreditation approach will significantly improve care for IDUs by:

- improving access to and quality of MMT programs;
- allowing for increased professional discretion and medical judgment in designing treatment plans based on individual needs, especially in managing methadone doses and length of treatment, and whether withdrawal from medication is possible or desirable;
- helping to move MMT closer to the mainstream of health care practice (this increase in the range of settings may increase MMT in physicians' offices and increase interest by hospitals and HMOs in providing these services);
- improving oversight and accountability and helping to promote state-of-the-art treatment services; and
- enhancing patient rights and patient responsibilities.

### To Learn More About This Topic

Read the overview fact sheet in this series on drug users and substance abuse treatment – "Substance Abuse Treatment for Injection Drug Users: A Strategy with Many Benefits." It provides basic information, links to the other fact sheets in this series, and links to other useful information (both print and web).

Visit websites of the Centers for Disease Control and Prevention ([www.cdc.gov/idu](http://www.cdc.gov/idu)) and the Academy for Educational Development ([www.health-strategies.org/pubs/publications.htm](http://www.health-strategies.org/pubs/publications.htm)) for these and related materials:

- *Preventing Blood-borne Infections Among Injection Drug Users: A Comprehensive Approach*, which provides extensive background information on HIV and viral hepatitis infection in IDUs and the legal, social, and policy environment, and describes strategies and principles of a comprehensive approach to addressing these issues.
- *Interventions to Increase IDUs' Access to Sterile Syringes*, a series of six fact sheets.
- *Drug Use, HIV, and the Criminal Justice System*, a series of eight fact sheets.

### Visit these websites:

- The Substance Abuse and Mental Health Services Administration, to learn more about the new federal regulations governing methadone treatment programs: [www.samhsa.gov/news/news.html](http://www.samhsa.gov/news/news.html) (click on Archives of News Releases and scroll down to the two May 18, 2001 releases)
- The Addiction Treatment Forum, which publishes newsletters and other information on substance abuse and addiction research, therapies, news: [www.atforum.com/](http://www.atforum.com/)
- The American Methadone Treatment Association: [www.americanmethadone.org/](http://www.americanmethadone.org/)

See the October/November 2000 and January 2001 issues of the *Mt. Sinai Journal of Medicine*. The 14 papers in these two theme issues focus on a wide range of issues related to methadone maintenance treatment and its impact on IDUs, including those infected with HIV or hepatitis C. *Mt. Sinai Journal of Medicine* 2000;67(5&6) [www.mssm.edu/msjournal/67/6756.shtml](http://www.mssm.edu/msjournal/67/6756.shtml) and 2001;68(1) [www.mssm.edu/msjournal/68/681.shtml](http://www.mssm.edu/msjournal/68/681.shtml)

### Check out these sources of information:

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Department of Health and Human Services

<http://www.cdc.gov/idu>

Through the Academy for Educational Development (AED), IDU-related technical assistance is available to health departments funded by CDC to conduct HIV prevention and to HIV prevention community planning groups (CPGs). For more information, contact your CDC HIV prevention project officer at 404-639-5230 or AED at (202) 884-8952.



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UPDATED JUNE 2004

DSHS Research and Data Analysis Division, 4.49fs

## Methadone Treatment For Opiate Addiction Lowers Health Care Costs And Reduces Arrests And Convictions

WASHINGTON STATE SUPPLEMENTAL SECURITY INCOME RECIPIENTS

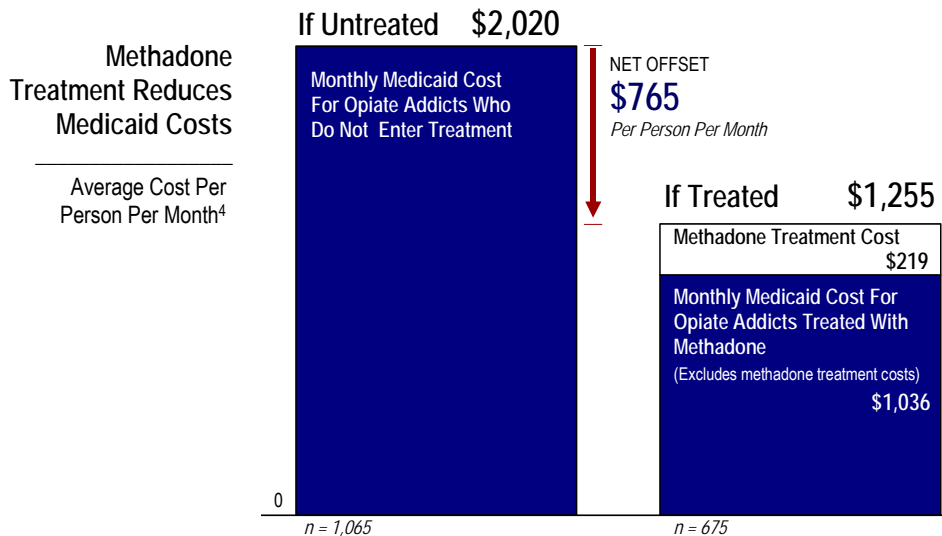
### Methadone Treatment Results In Lower Health Care Costs

Medicaid-paid medical, mental health, and long-term care costs are significantly lower for persons addicted to opiates who participate in methadone treatment, compared to opiate addicts who remain untreated.<sup>1</sup>

These cost offsets can be interpreted as **costs avoided** for clients already receiving treatment, and as **potential savings** that might be realized by treating the untreated.

- The **average net cost offset is \$765** per person per month for methadone treatment for opiate addiction.
- The average methadone **treatment cost is \$219** per person per month.<sup>2</sup>
- **Reduced medical costs account for 80 percent** of the offset.<sup>3</sup>

The chart below compares the monthly Medicaid costs for opiate addicts who do not enter treatment with costs for opiate addicts who participate in methadone treatment.



<sup>1</sup> Mental health costs include state psychiatric hospital, community psychiatric hospital, and outpatient mental health expenditures. Long-term care expenditures include nursing home costs. Costs reported are generally Medicaid-paid claims receiving 50/50 state/federal match. Mental health costs include some "state-only" dollars.

<sup>2</sup> The standard rate for methadone treatment is about \$10 per day; however, the average cost presented here includes those who were not in treatment for the entire follow-up period, bringing down the overall average cost per month to \$219.

<sup>3</sup> Non-medical cost offsets include reductions in mental health (state psychiatric, community psychiatric, outpatient mental health), and nursing home costs.

<sup>4</sup> Cost offsets were estimated using regression models in which the effects of covariates (age, gender, race/ethnicity, baseline medical expenditures, dual eligible status) were controlled.

## Longer Stays In Methadone Treatment Result In The Greatest Cost Offset

Cost offsets were examined for different lengths of time spent in treatment. It was found that longer stays in methadone treatment result in the greatest reductions.

- For treatment stays up to 90 days, the **average monthly offset is \$725** for persons treated with methadone.
- For methadone treatment stays over 365 days, the Medicaid **cost offset averages \$899** per person per month.



### ABOUT METHADONE TREATMENT

Methadone Treatment – or “opiate substitution” treatment – is an outpatient service for individuals addicted to heroin or other opiates. Under this approach, state-funded and accredited opiate substitution treatment agencies provide counseling and daily or near-daily administration of methadone or other approved substitute drugs. Patients also receive education, random urine drug screening to monitor drug use, and are subject to stringent rules regarding compliance. Methadone treatment is distinct from “drug free” treatment for opiate addiction. “Drug free” programs do not dispense methadone or other approved substitute drugs to persons addicted to opiates. A “drug free” treatment program may occur in a residential or outpatient setting. Residential modalities are generally highly structured and include intensive inpatient and long-term residential treatment. Intensive inpatient treatment typically lasts 21 to 28 days while long-term residential treatment lasts 90 days or longer.

Compared to clients receiving “drug free” treatment for opiate addiction, clients in methadone treatment tend to have more years of regular heroin use prior to treatment, more intense use of heroin in the 30 days prior to treatment, and greater dependence on income acquired through illegal activity.<sup>6</sup>

<sup>5</sup> Cost offsets were estimated using regression models in which the effects of covariates (age, gender, race/ethnicity, baseline medical expenditures, dual eligible status) were controlled. Cost offsets are measured relative to untreated clients.

<sup>6</sup> Carney, M., Elworth, J., Calsyn, D., Kivlahan, D., Peavy, M., Floyd, A., and Donovan, D., 2003. *Washington State Outcomes Project: Opiate Study Sample (Final Report)*. University of Washington Alcohol and Drug Abuse Institute, University of Washington Department of Psychiatry, and VA Puget Sound Health Care System, Seattle Division, October 2003.



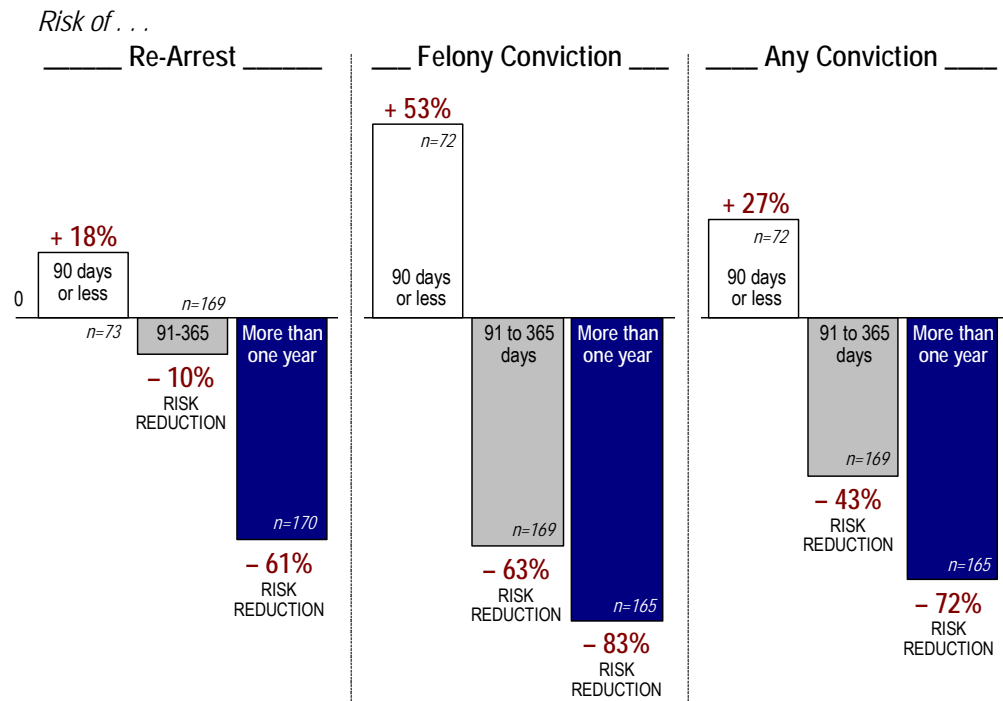
## Longer Stays In Methadone Treatment Reduce The Risk Of Criminal Re-Arrest And Conviction

Stays in methadone treatment of more than 90 days are associated with a reduced risk of re-arrest or conviction. Methadone treatment stays over one year are associated with particularly dramatic reductions. Staying in methadone treatment 90 days or less is associated with an increased risk of re-arrest or conviction, which may reflect the effect of arrests or convictions in terminating treatment, or increased criminal activity that may follow relapse in use and premature exit from treatment.

- Compared to untreated opiate addicts, the risk of re-arrest is 18 percent higher for persons who stay in methadone treatment for 90 days or less, but is **10 percent lower** for those in treatment 91 to 365 days and **61 percent lower** for those who stay more than one year.<sup>7</sup>
- Compared to untreated opiate addicts, the risk of a felony conviction is 53 percent higher for persons in methadone treatment for 90 days or less, **63 percent lower** for opiate addicts in methadone treatment 91 to 365 days, and **83 percent lower** for those in methadone treatment for more than one year.
- Similarly, the risk of any conviction is 27 percent higher for persons who stay in methadone treatment for 90 days or less, **43 percent lower** for opiate addicts in methadone treatment 91 to 365 days, and **72 percent lower** for those who stay in methadone treatment for more than one year.

## Criminal Justice Outcomes Improve With Longer Stays In Methadone Treatment

Risk relative to untreated clients with opiate addiction



<sup>7</sup> Percentages reflect the change in the hazard of re-arrest or conviction, relative to untreated clients. Estimates are from proportional hazards models that control for age, gender, and race/ethnicity. The zero axis represents the baseline risk for the untreated.

### TECHNICAL NOTES

This paper examines “cost offsets” – costs avoided for clients already receiving treatment or potential savings that might be realized by treating the untreated – of Medicaid medical, mental health, and long-term care costs among opiate addicts who were treated with methadone. The paper also examines criminal arrest and conviction outcomes among persons addicted to opiates who enter methadone treatment. The criminal justice analyses are restricted to clients with prior criminal histories.

The study population included clients who received Supplemental Security Income (SSI) benefits at some time between July 1997 and December 2001 and who were identified as having a substance abuse problem based on administrative records. The SSI program provides cash and medical assistance to persons with little or no income who are unable to work due primarily to disability. Results of the original study<sup>8</sup> and comparisons for stimulant drug abusers<sup>9</sup> and those with opiate addictions who participated in drug free chemical dependency treatment<sup>10</sup> are also available from the authors.

The need for treatment for these clients was identified through events recorded in administrative data. Information used to identify a need for treatment included medical diagnoses or procedures; detoxification, assessment, or alcohol or drug (AOD) treatment encounters; and arrests for drug or alcohol-related offenses. Clients were included in the analysis only if they had at least one month of medical assistance eligibility both before and after the “index event” indicating a need for AOD treatment.

For this report, a subset of 3,354 persons was identified as opiate-dependent by the presence of:

- Heroin, non-prescription methadone, prescribed opiate substitutes, or other opiates and synthetics as primary, secondary, or tertiary drug of abuse in TARGET records.<sup>11</sup>
- Diagnosis of opiate abuse or dependence in Medicaid claims data.

Medicaid costs of opiate-addicted clients receiving methadone treatment were compared with costs of opiate-addicted clients who remained untreated. Offsets were estimated using regression models to control for the effects of covariates such as age, gender, race/ethnicity, and baseline medical expenditures.

<sup>8</sup> Estee, S. and Nordlund, D., 2003. *Washington State Supplemental Security Income (SSI) Cost Offset Pilot Project: 2002 Progress Report*. Washington State Department of Social and Health Services, Research and Data Analysis Division, February.

<sup>9</sup> Nordlund, D., Estee, S. and Yamashiro, G., 2003. *Treatment of Stimulant Addiction Including Addiction to Methamphetamine Results in Lower Health Care Costs and Reduced Arrests and Convictions: Washington State Supplemental Security Income Recipients*. Washington State Department of Social and Health Services, Research and Data Analysis Division, December.

<sup>10</sup> Nordlund, D., Estee, S., Mancuso, D. and Felver, B., 2004. *Non-Methadone Chemical Dependency Treatment for Opiate Addiction Reduces Health Care Costs, Arrests and Convictions: Washington State Supplemental Security Income Recipients*. Washington State Department of Social and Health Services, Research and Data Analysis Division, March.

<sup>11</sup> TARGET is the database maintained by the Division of Alcohol and Substance Abuse that contains a record of all publicly funded chemical dependency treatment in Washington State.

Additional copies of this fact sheet may be obtained from the following websites:

<http://www1.dshs.wa.gov/RDA/> or <http://www1.dshs.wa.gov/dasa/>

or through the Washington State Alcohol/Drug Clearinghouse by calling 1-800-662-9111 or 206-725-9696 (within Seattle or outside Washington State), by e-mailing [clearinghouse@adhl.org](mailto:clearinghouse@adhl.org), or by writing to 6535 Fifth Place South, Seattle, Washington 98108-0243.



Research and Data Analysis Division  
Report Number 4.49fs



# Populations at risk for opioid overdose

**Len Paulozzi, MD, MPH**

Division of Unintentional Injury Prevention  
National Center for Injury Prevention and Control  
Centers for Disease Control and Prevention  
April 12, 2012



# OVERVIEW OF PRESENTATION

**Trends**

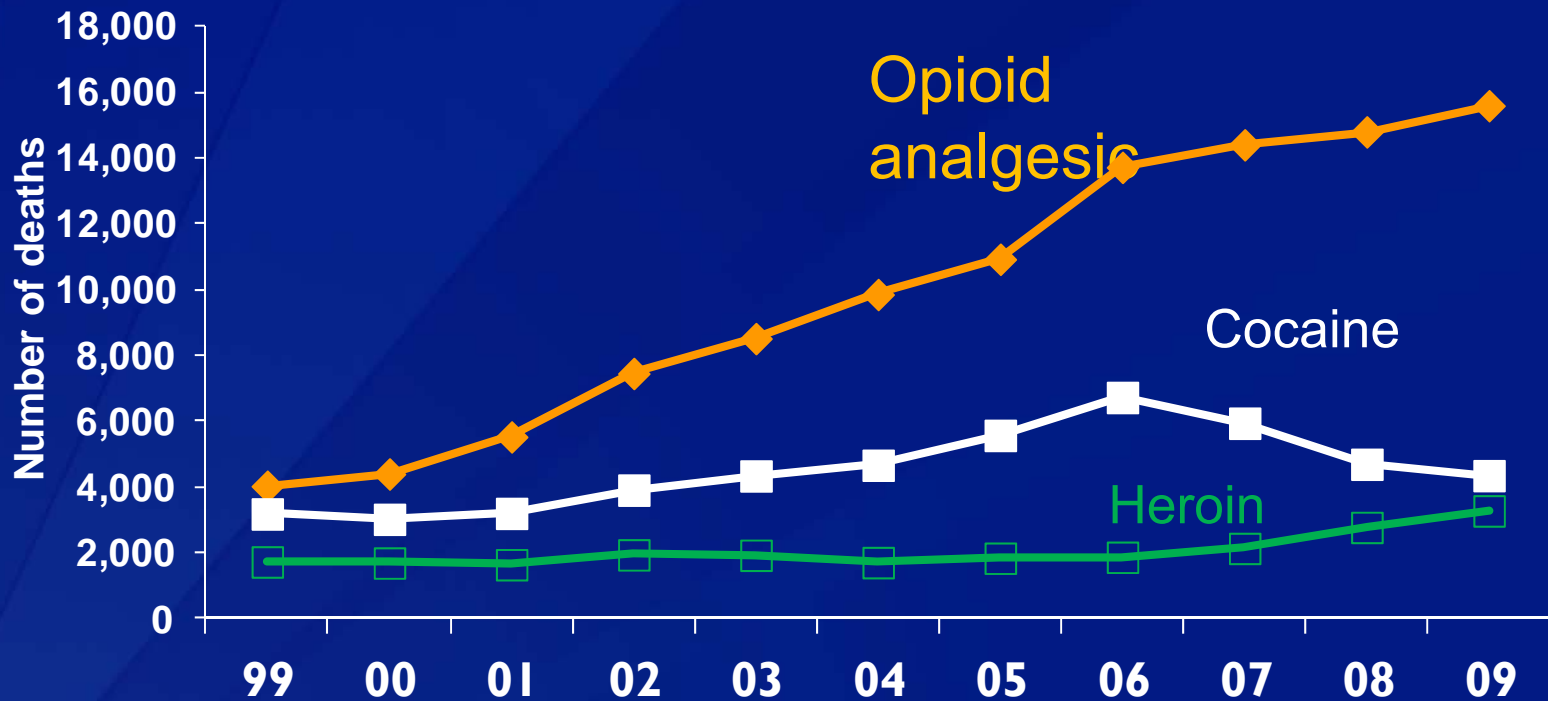
**Risk factors**

**Demographic variables**

**Other personal characteristics as risks**

**Prescription history as a risk**

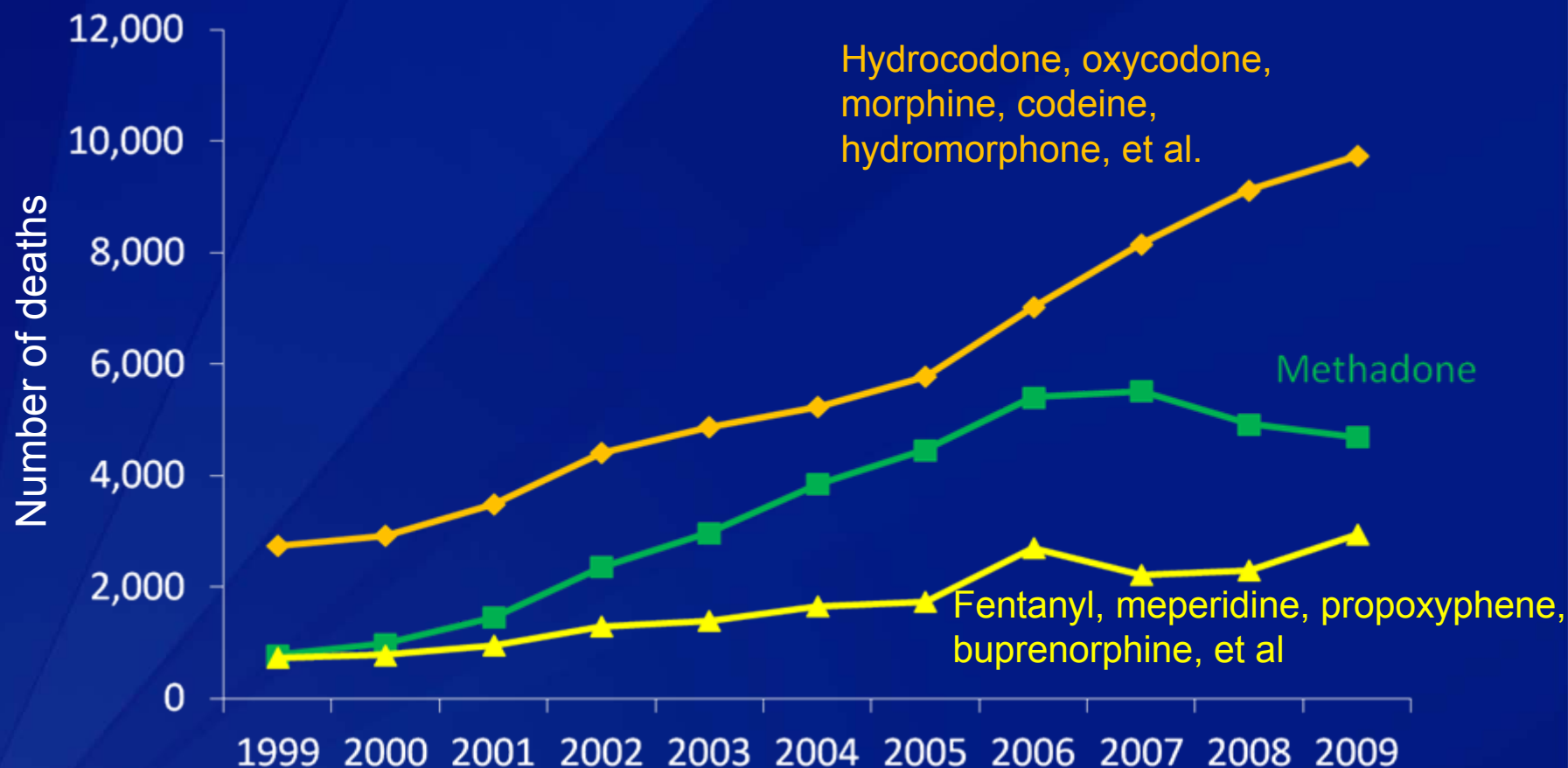
# Drug overdose deaths of all intents by major drug type, U.S., 1999-2009



Source: National Vital Statistics System. The reported 2009 numbers are underestimates. Some overdose deaths were not included in the total for 2009 because of delayed reporting of the final cause of death.



# Drug overdose deaths of all intents by type of opioid analgesic involved, U.S., 1999-2009



Source: National Vital Statistics System. The reported 2009 numbers are underestimates. Some overdose deaths were not included in the total for 2009 because of delayed reporting of the final cause of death.

# OVERVIEW OF PRESENTATION

**Trends**

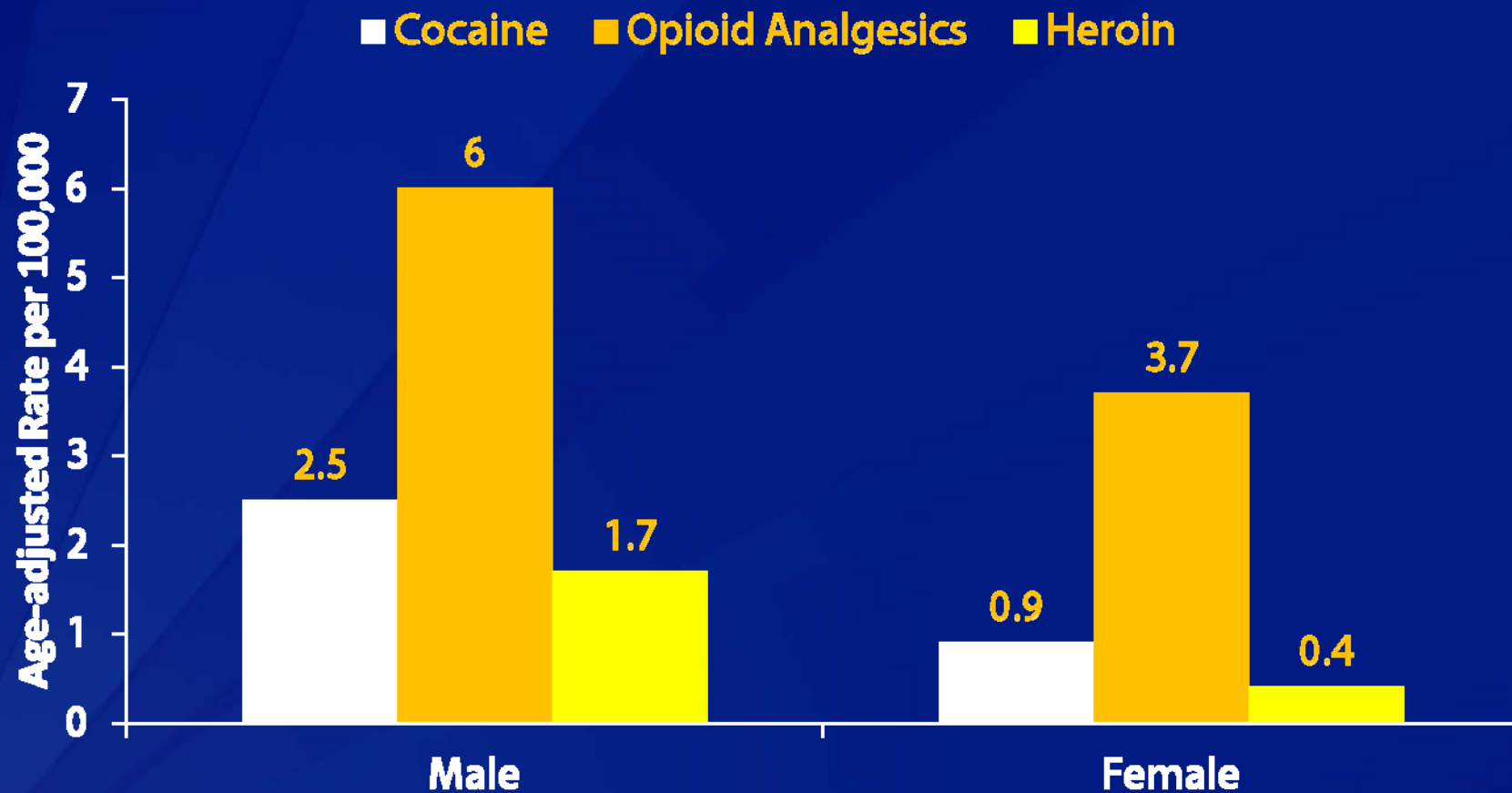
**Risk factors**

**Demographic variables**

**Other personal characteristics as risks**

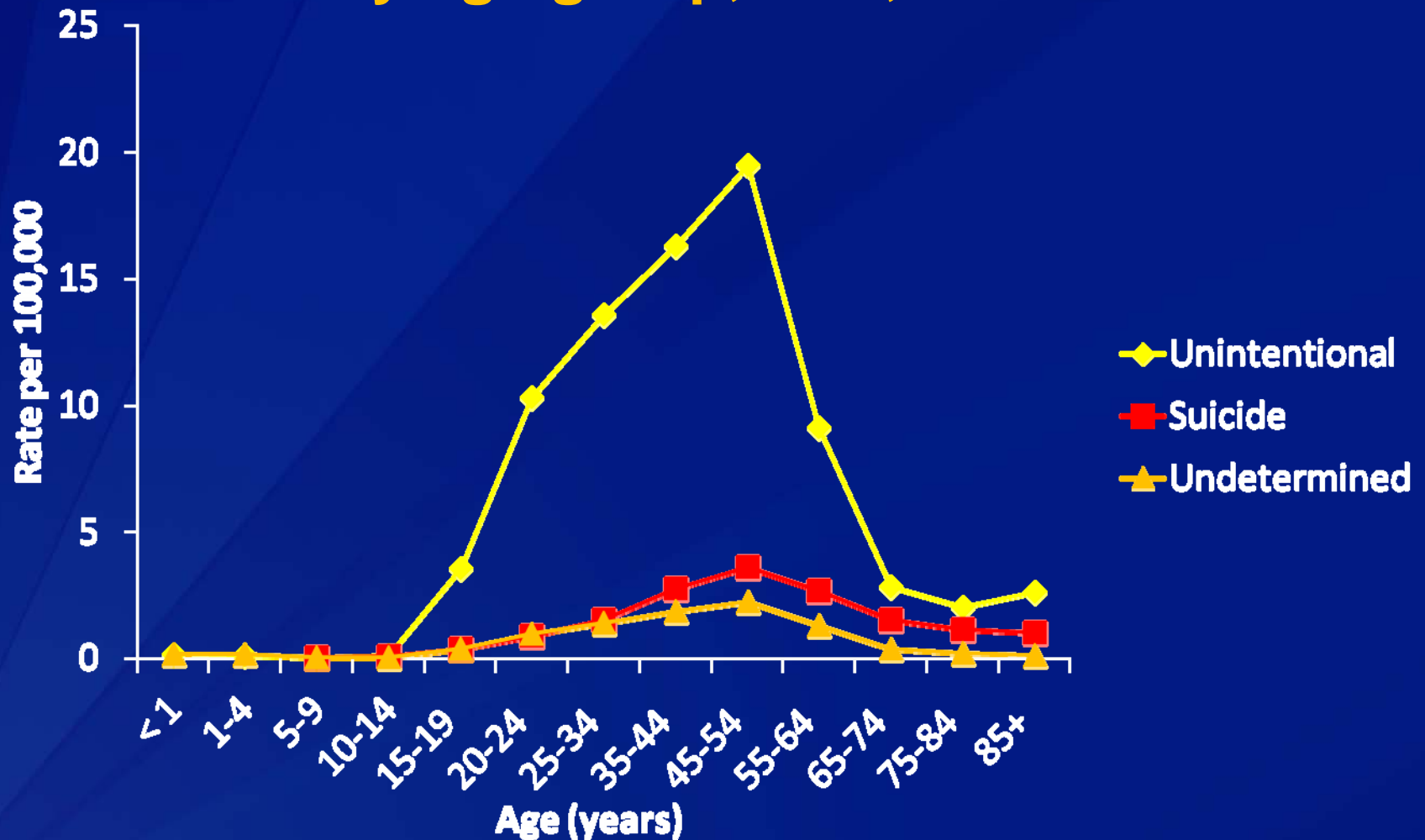
**Prescription history as a risk**

# Drug overdose death rates by sex and drug type, U.S., 2008



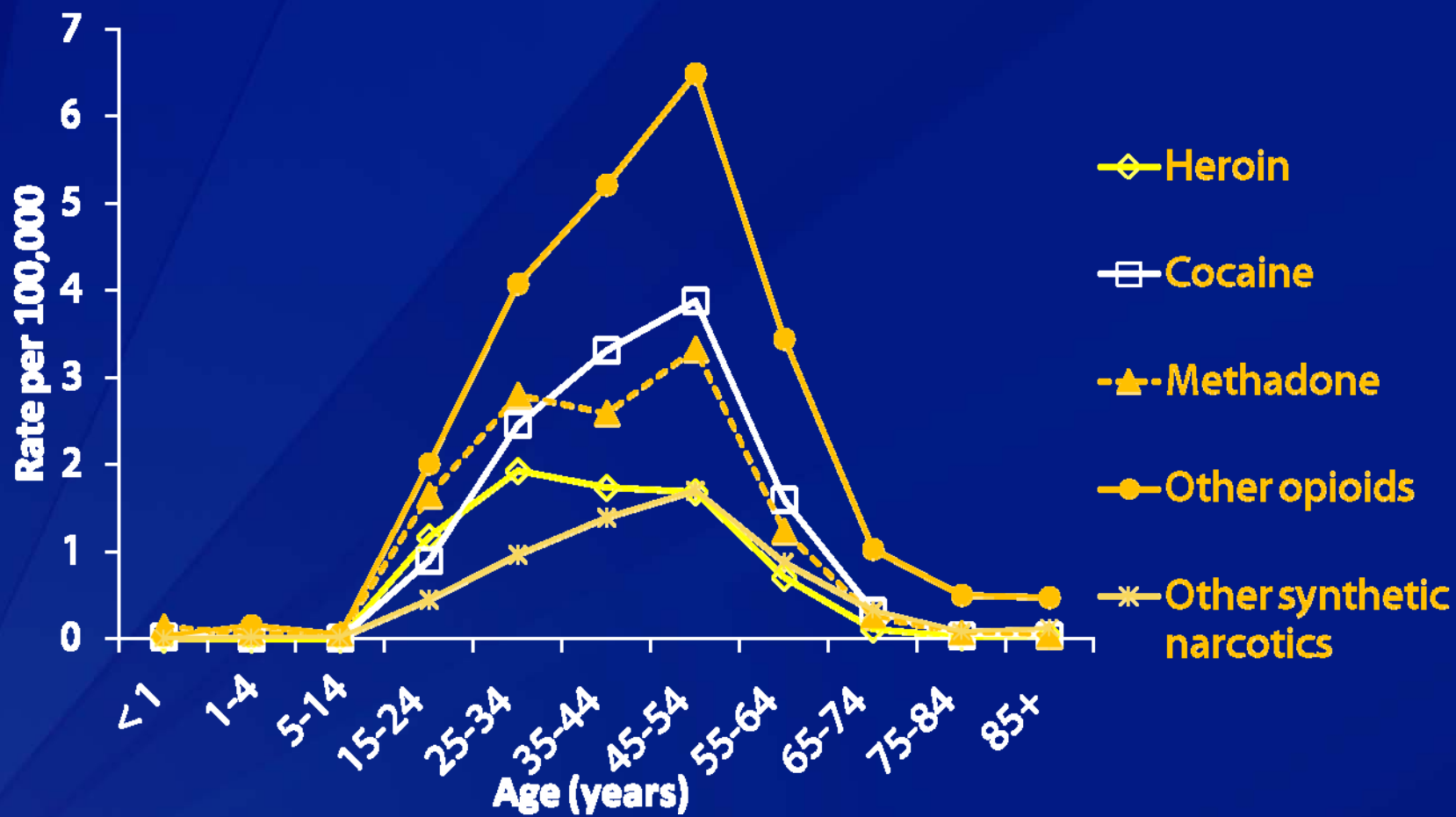
Source: National Vital Statistics System

## Drug overdose death rates by intent by age group, U.S., 2008



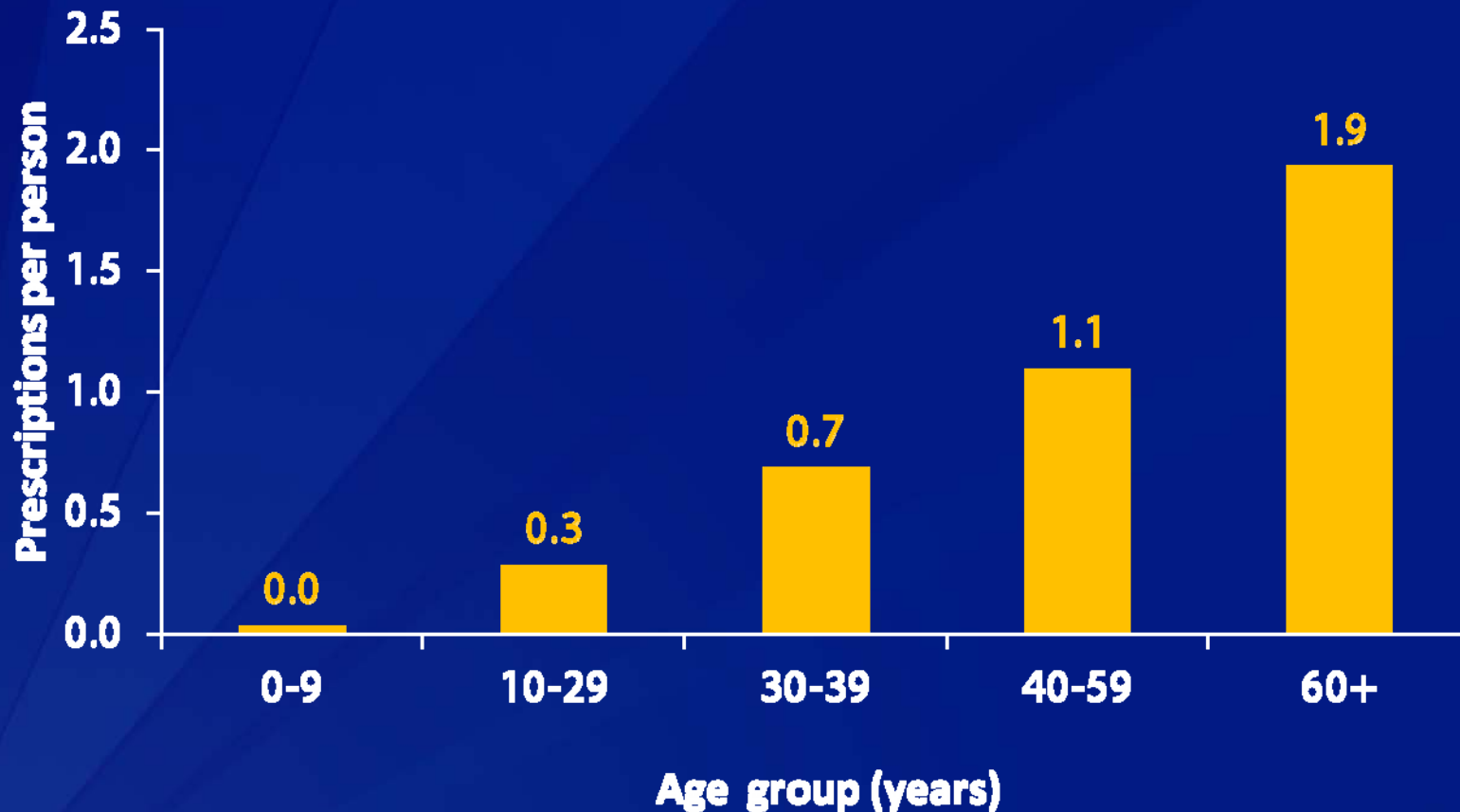
Source: National Vital Statistics System

# Drug overdose death rates by drug type by age group, U.S., 2008



Source: National Vital Statistics System

# Opioid prescriptions per person by age group, U.S., 2009

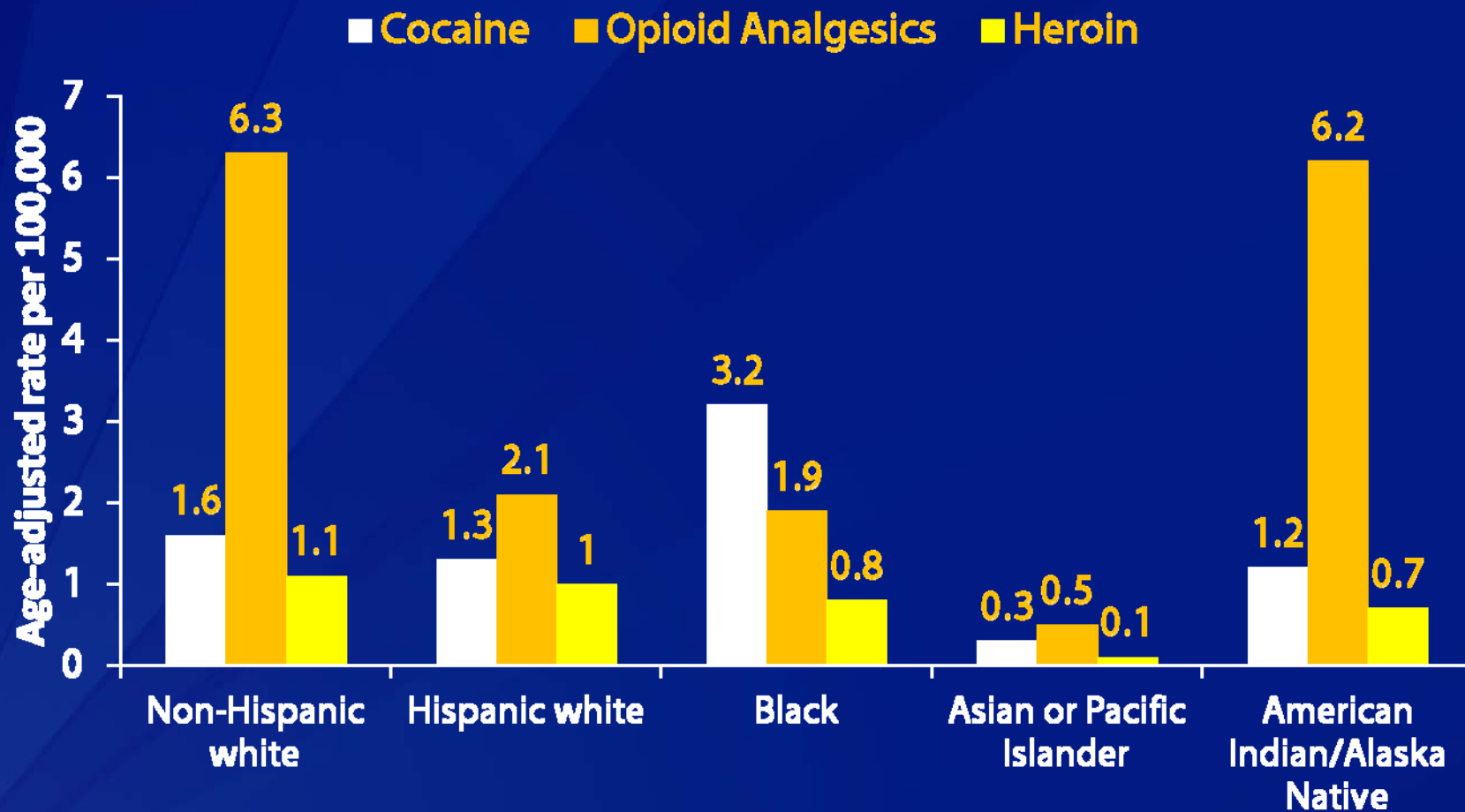


Source: Volkow et al. JAMA 2011;305:1299-1301



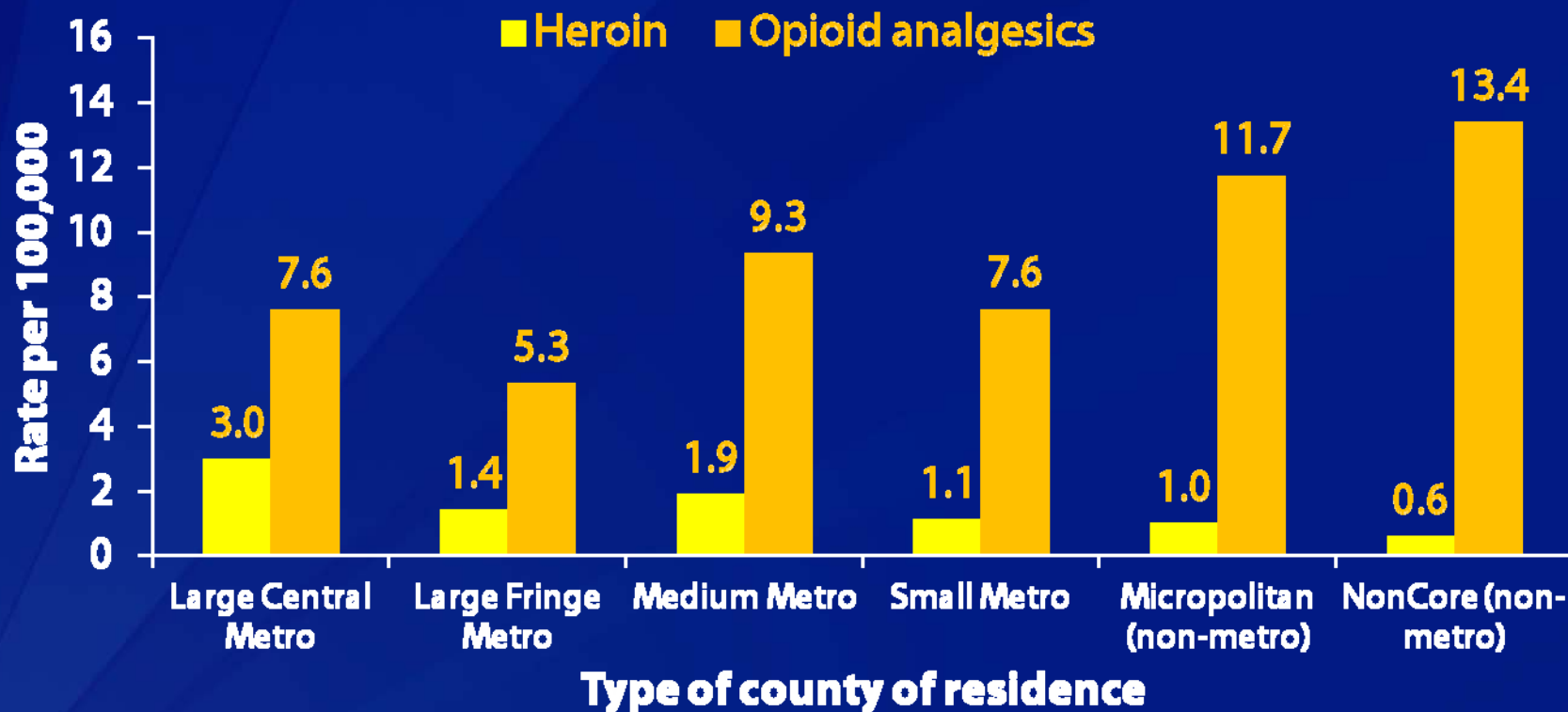


# Drug overdose death rates by race/ethnicity and drug type, U.S., 2008



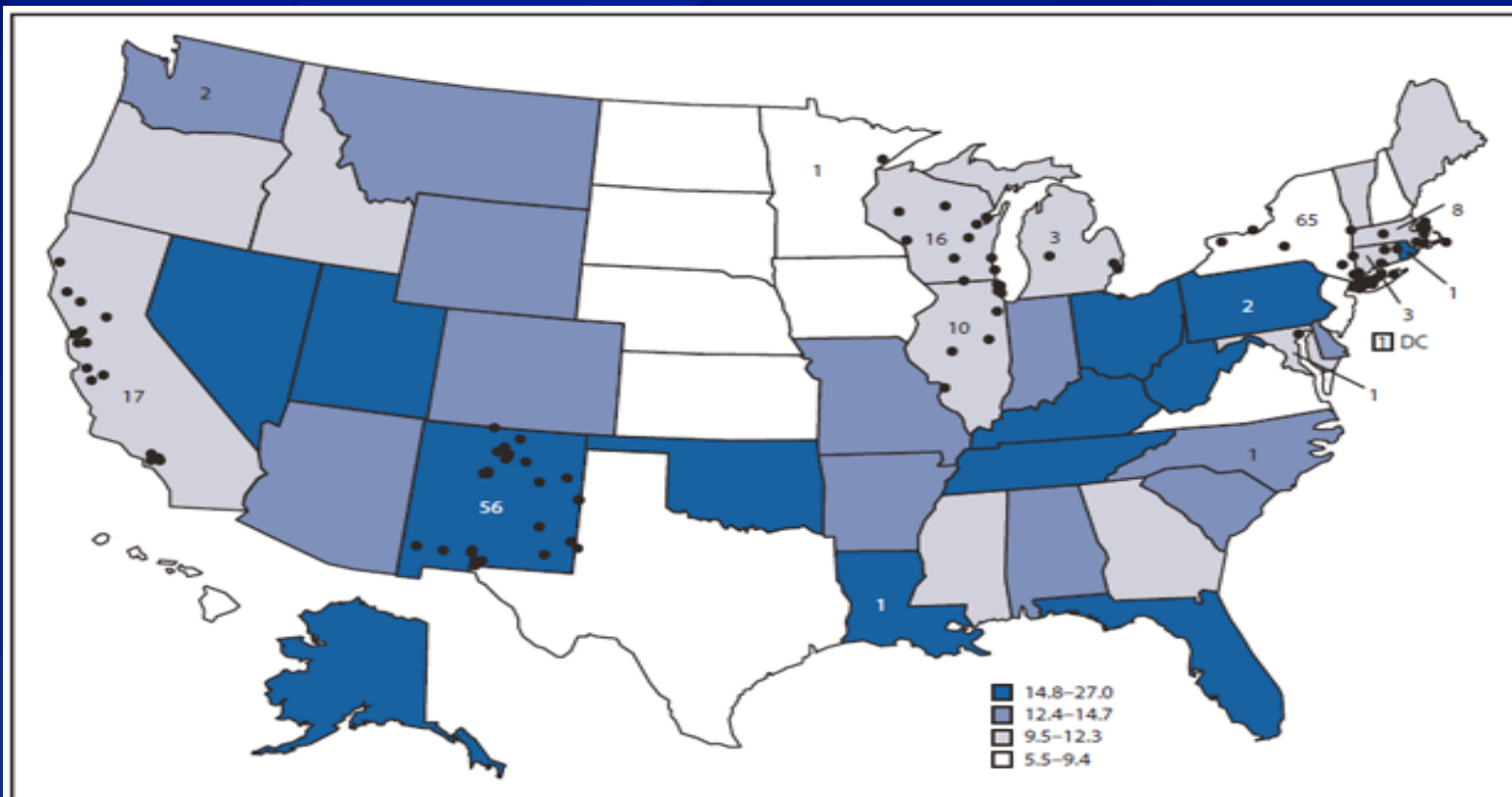
Source: National Vital Statistics System

# Drug overdose death rates by urbanization and drug type, 16 states with centralized medical examiner systems, U.S. whites, 2008



Source: National Vital Statistics System

# Drug overdose death rates<sup>¶</sup> in 2008 and number and location\* of drug overdose prevention programs providing naloxone in 2010



Source: Wheeler et al, **Community-based opioid overdose prevention programs providing naloxone — United States, 2010**

MMWR 2012;61:101

<sup>¶</sup>Per 100,000 population. All intents included.

\*Not shown in states with fewer than three local programs.

# OVERVIEW OF PRESENTATION

Trends

Risk factors

Demographic variables

**Other personal characteristics as risks**

**Prescription history as a risk**



## Characteristics of unintentional pharmaceutical overdose deaths (N=295), West Virginia, 2006

Characteristic	Pct.
History of substance abuse	78.3
Other mental illness	42.7
Nonmedical route of administration	22.4
Previous overdose	16.9
TOTAL	100.0

Sources: Hall et al, JAMA, 2008 and Toblin et al, J Clin Psych, 2010

## Characteristics of unintentional prescription opioid overdose deaths (N=155), Utah, 2008-9

Characteristic	Pct.
History of substance abuse	60
Signs of nonmedical use (e.g., use without rx)	51
History of chronic pain	82
Mental illness diagnosed by a provider	57
TOTAL	100

Source: Presentation by WA Lanier at 2010 CDC EIS Conference, Atlanta, GA

# Low income as risk for fatal prescription opioid overdose

Exposure	Referent	RR	(95% CI)	Source
Residence in a WV county with 22-39% of the population in poverty	Residence in a WV county with 9-16% of the population in poverty	2.1	(1.5-2.9)	Hall, 2008
Medicaid-enrolled WA residents	Non-Medicaid-enrolled WA residents	5.7	(5.3-6.1)	Coolen, 2009

Sources: Hall et al, JAMA, 2008;300:2613; Coolen et al, MMWR, 2009;58:1171-1175

## Mental health problems as risks for opioid overdose (fatal or nonfatal)

Exposure	RR/HR	(95% CI)	Source
Substance abuse diagnosis in patients on chronic opioid therapy	2.6	Not provided	Dunn, 2010
Substance use disorder in chronic pain patients	2.5	(2.0-3.2)	Bohnert, 2011
Depression diagnosis in patients on chronic opioid therapy	3.1	Not provided	Dunn, 2010
Psychiatric disorders other than substance abuse in chronic pain patients	1.9	(1.5-2.4)	Bohnert, 2011

Dunn, Ann Intern Med 2010;152:85-92. Braden, Arch Intern Med 2010;170:1425. Bohnert, JAMA 2011;305:1315-1321.



## Lack of prescription for involved drugs among unintentional pharmaceutical overdose deaths, various states

Type of Overdose Death	State/year	Pct w/o Rx
Pharmaceutical	WV 2006	63%
Prescription opioid	OH 2006-08	25%
Unintentional opioid	UT 2008-09	37%
Methadone in Medicaid population	NC 2007	74%
Methadone	OH 2006-08	71%

# OVERVIEW OF PRESENTATION

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**Prescription history as a risk**

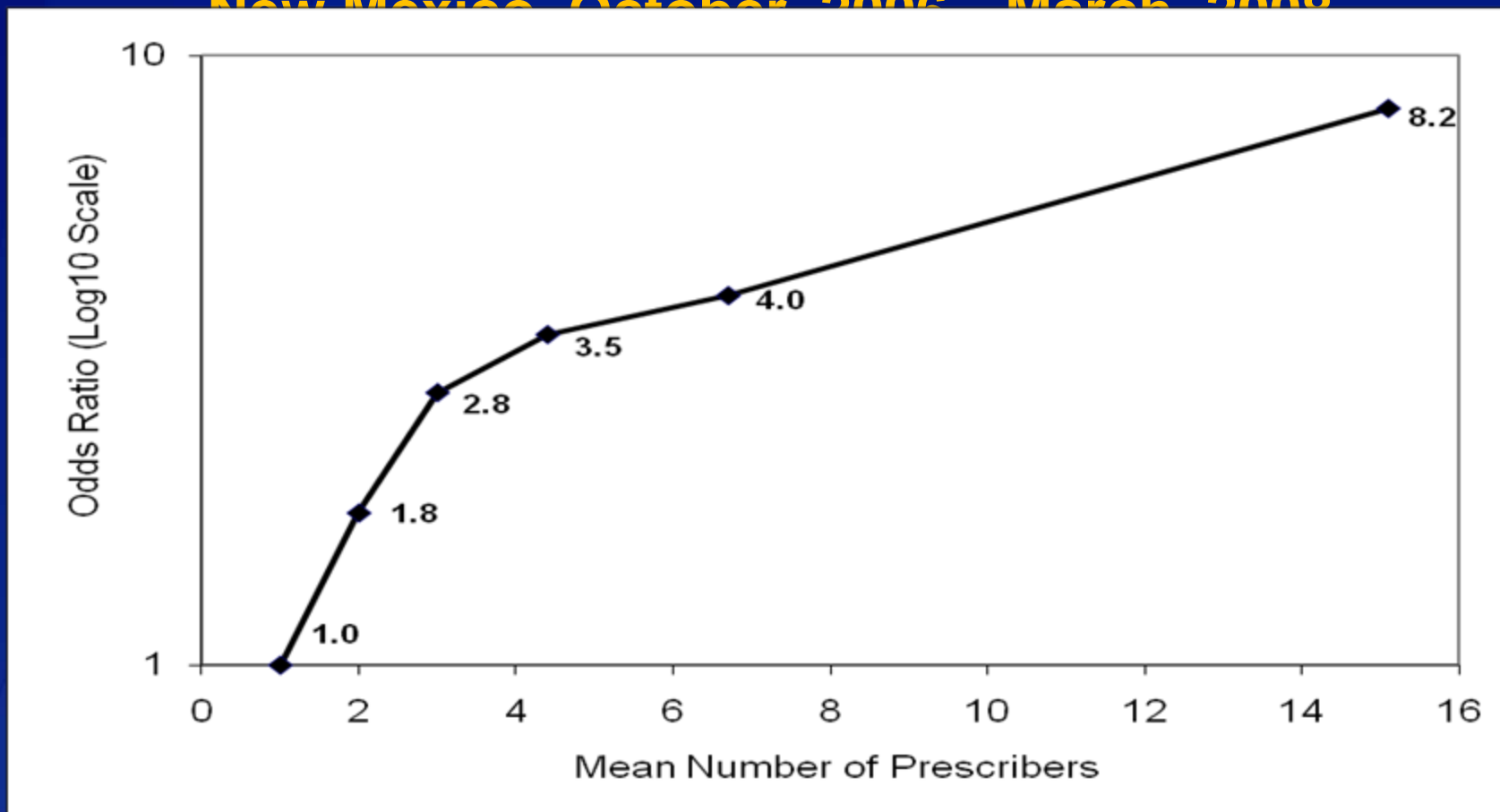
# Use of multiple prescribers (“doctor shopping”) by people dying of prescription overdoses

Definition of doctor shopping	State Year	Pct.
Filled prescriptions from an average of five prescribers/year over 3 years (N=1,047)	Ohio 2006-08	16%
Filled prescriptions from 5+ prescribers in preceding year (N=295)	WV 2006	21%

Source: Ohio Department of Health at [www.healthyohioprogram.org/diseaseprevention/dpoison/drugdata.aspx](http://www.healthyohioprogram.org/diseaseprevention/dpoison/drugdata.aspx) and Hall et al, JAMA, 2008 and Toblin et al, J Clin Psychiatry, 2010

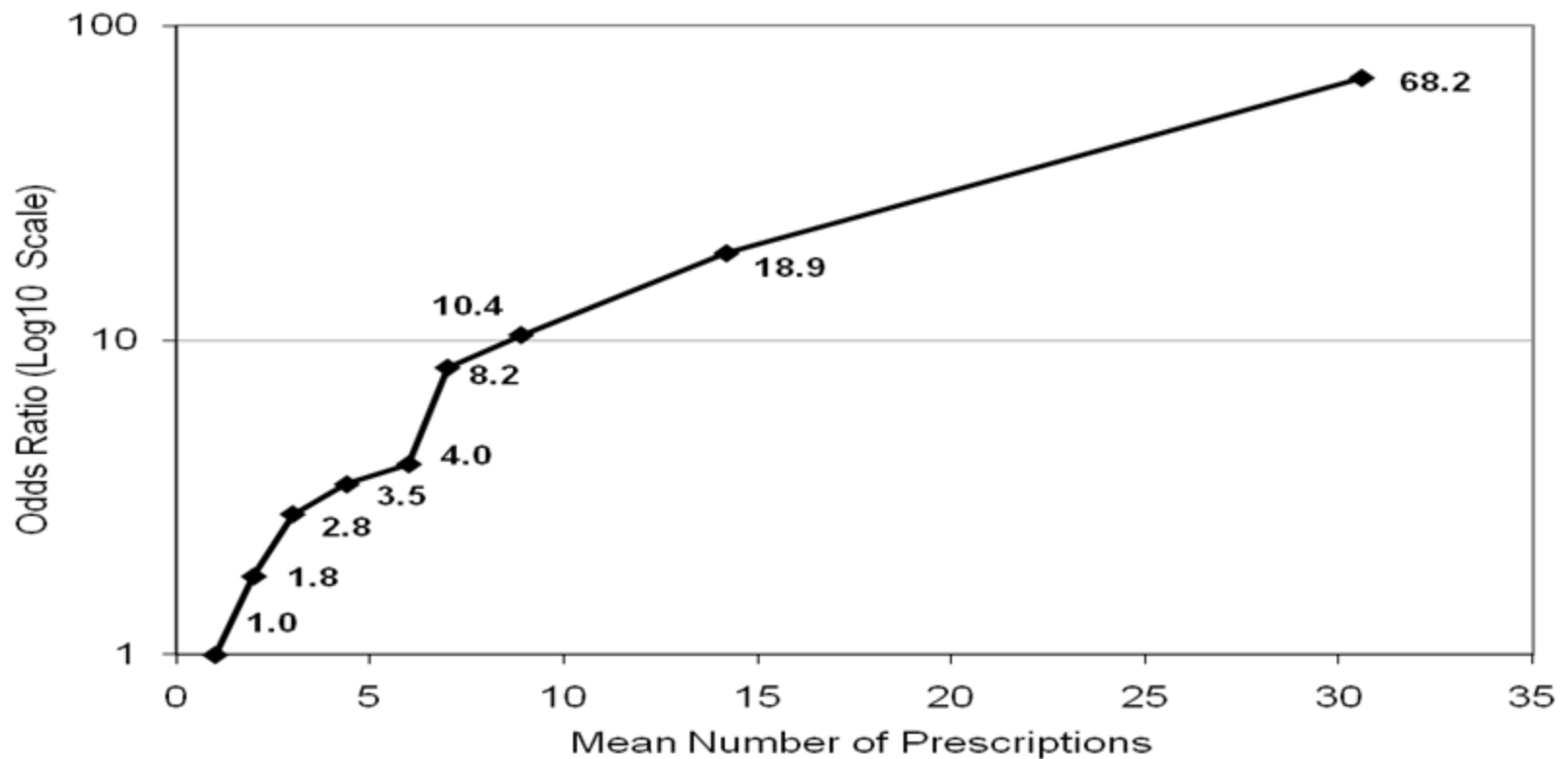
# Crude association of number of prescribers per patient with risk of unintentional drug overdose death,

New Mexico, October 2006–March 2008



During six months prior to death. Source: Paulozzi, et al. Pain Med 2012; 13:87-95

# Crude association of number of prescriptions for controlled substances per patient with risk of unintentional drug overdose death, New Mexico, October, 2006—March, 2008



During six months prior to death. Source: Paulozzi, et al. Pain Med 2012; 13:87-95

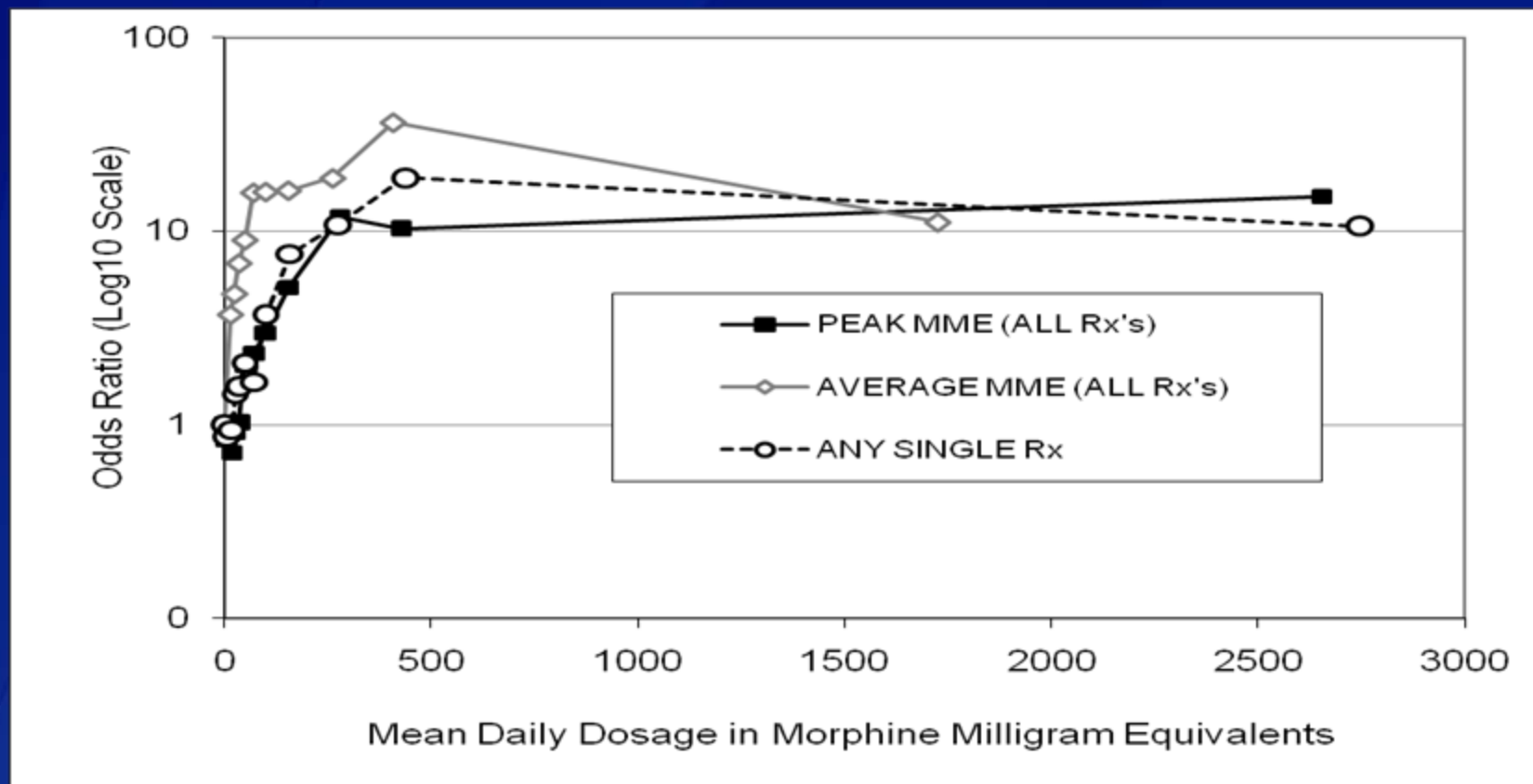
## Daily dosage of opioid analgesic as risk for overdose

Exposure (morphine mg equivalents/day)	Referent exposure	RR/O R	(95% CI)	Source
≥ 100	No recent use	8.8	(3.4-19.7)	Dunn, 2010
>120	< Median	1.08	(1.02-1.1.15)	Braden, 2010
≥ 100	1- <20	7.18	(4.85-10.65)	Bohnert, 2011
>400	≤ 200	6.1	Not provided	Gomes, 2011
>120	≤120	7.6	(5.8-10.0)	Paulozzi, 2012

Dunn, Ann Intern Med 2010;152:85-92. Braden, Arch Intern Med 2010;170:1425. Bohnert, JAMA 2011;305:1315-1321. Gomes Open Med 2011;5:E20. Paulozzi, Pain Med 2012;13:87-95



# Crude association of daily dosage of opioid analgesics with risk of unintentional drug overdose death, New Mexico, October, 2006—March, 2008



During six months prior to death. Source: Paulozzi, et al. Pain Med 2012; 13:87-95

# Summary of potential markers for risk of opioid overdose

## □ Demographic

- Male sex
- Age:
  - 45-54 years old (opioid analgesic)
  - 25-34 (heroin)
- Non-Hispanic white race
- Urbanization:
  - non-metro county (opioid analgesic)
  - metro county (heroin)
- Low income/Medicaid
- State of residence

## □ Personal characteristics

- Substance abuse
- Other mental health diagnosis
- Nonmedical use of prescription
- Route of administration

## □ Prescription history

- Multiple prescriptions
- Multiple prescribers
- High daily dosage



# Thank you

- **The findings and conclusions in this report are those of the author and do not necessarily represent the official position of the Centers for Disease Control and Prevention**

# ALARMINGLY HIGH:

## *Prescription Drug Abuse and the Pill Pipeline in Appalachia*

ROBERT P. PACK



Over the past decade, prescription drug abuse has cut a destructive path through Appalachia. I've been a close witness to that destruction. I've seen friends and acquaintances struggle and die, youth and young adults turn to theft and prostitution, families weakened and destroyed, and whole towns transformed because of crime and violence.

One spring afternoon in 2002, I drove to Richwood, West Virginia, to do a focus group with teachers and community leaders on inhalant abuse—the huffing of gas, paint, and solvents to get high. I was a professor at the West Virginia University School of Medicine, and I had chosen to study inhalant abuse since West Virginia had the highest rate of youth “huffing” in the nation, about 40 percent above the national average. Over the course of the afternoon, the group provided some polite interest and some pretty good answers to my questions. All was going well, and I was going on about the risks and long-term consequences of huffing when one of the participants raised his hand and said, “You know, huffing paint and gas is a problem for a few kids around here. I have known one or two that had that problem. But, if you really want to help, you’ll come to the local Narcotics Anonymous meeting with us this evening and hear about our real problem.”

And so I went. At that meeting I heard stories that defy logic, tradition, culture, stereotypes, and sanity. Stories of housewives selling everything they own, including their bodies; stories of rural kingpins, invisible networks, and trips to Florida, Mexico, and

Baltimore; and stories of friends and acquaintances whose lives ended tragically.

I spent the two-hour drive back to Morgantown that night in silence. If what they said was happening in their community was true, then we had a coming storm on our hands.

Truth be told, the storm was already raging. On the national level, celebrity pill addiction and overdose were beginning to be popular news stories. But our Appalachian story was altogether different. I started paying attention to the news in our region and started seeing dozens of articles about pill diversion, pharmacy theft, and overdoses. Meanwhile, my childhood friend, with whom I kept up regularly on the phone and with whom I visited frequently when home, dropped the bomb that he had a serious problem and needed help.

We started spending more time on the phone. Indeed, over the next few years we would spend dozens of nights talking about his addiction, and it was a shocking education for me. My friend had become a full-time doctor shopper and pill trader. He had an enormous physiologic need for pills, taking at least sixty a day, in carefully regimented sequences, to offset or enhance effects and side-effects. He was brilliant, and he was desperate. We talked about treatment and counseling. We talked about the effect his addiction was having on his family. We talked about risks and desperation. In retrospect, I wish I had driven to his house, put him in the car, and gone with him to the hospital myself. I didn’t hear from him for several weeks, and I assumed all was going well after a recent

*Photo courtesy Charlie Warden.*

commitment to sobriety. When I got the call . . . and my father told me he had died, my academic curiosity instantly became a personal mission.

## Epidemiology

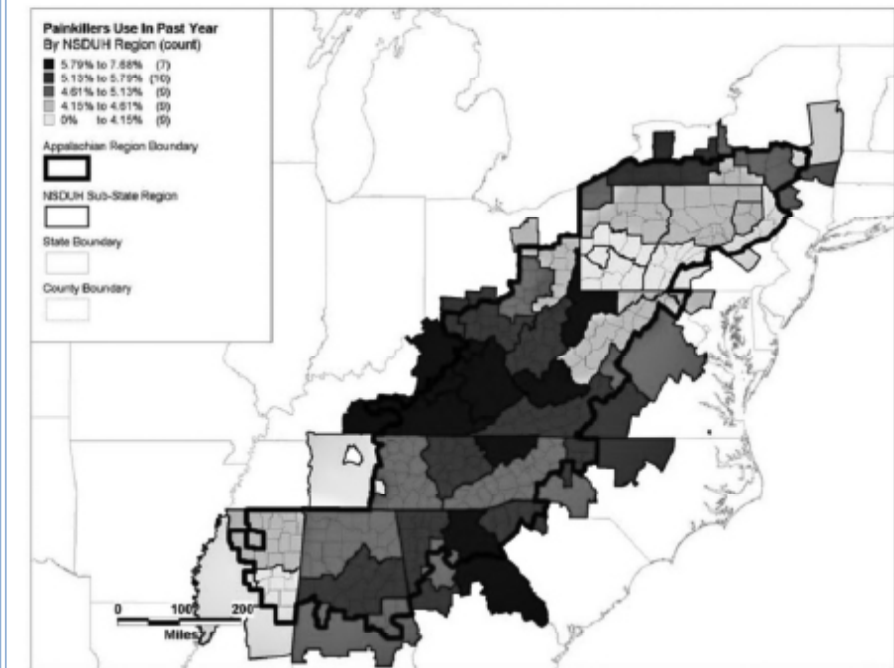
According to the National Household Survey of Drug Use and Health, more than 30 million Americans have abused prescription pills in their lifetime, about 15 million have done so in the past year, and about 7 million are current, past-month abusers. Pills are the second most frequent “new” substance adults choose when they use drugs illicitly. They are the first most frequent new substance for youth. While the use of other drugs like marijuana and cocaine has decreased or stayed the same, illicit use of pills has increased by at least 30 percent in the past decade. The most frequently abused are pain pills such as oxycodone and hydrocodone, followed by sedatives, stimulants, and tranquilizers. Other regions of the country suffer from the same problem, to be sure; however, pill abuse is more prevalent in rural areas and in areas where there is more poverty and unemployment.

In one study of the problem in Appalachia, funded by the Appalachian Regional Commission (ARC) and performed by the National Opinion Research Center and East Tennessee State University, about 22,000 of the 19.4 million residents of the region were surveyed about their drug use. Researchers found that the region is consistent with the rest of the country in the misuse of pills: 5.6 and 5.9 percent respectively. But the Central and Southern Appalachian areas are higher: 6.4 and 6.2 percent respectively. Pockets of the region are incredibly hard-hit—especially coal-mining country (Figure 1). Rates of painkiller abuse in coal-mining regions approach 7.7 percent, and treatment rates for opiates are higher than the rest of the nation. Heroin use is presently lower than the rest of the country, but it is rising, specifically in coal-mining areas. While the phrase “Hillbilly Heroin” is used to describe OxyContin, Appalachia is increasingly having to contend with the real thing.

Admission to treatment from 2000 to 2004 for heroin abuse in people age twelve and older showed

a steady decline nationally, dropping from 15 percent to 14 percent. However, treatment centers in Appalachia reported a steady increase in heroin treatment admissions from 4 percent to nearly 10 percent over the same period.

Map 2.19 Painkiller Use in Past Year, by NSDUH Sub-Region, 2002-2005



One reason is cost. Prescription drugs run between fifty cents and one dollar per milligram, for pills ranging from two to eighty milligrams per dose, whereas heroin is five dollars to ten dollars per dose, depending on its quality and the local market. A recent report in the *Los Angeles Times* indicated that black tar heroin syndicates seek out areas of the country where the pill problem is greatest and therefore have the highest capacity for heroin market growth. One method used by the heroin dealers is to find the local Suboxone or methadone clinics and approach the clientele as they enter and exit.

Most alarming is the fact that youth perceive prescription drugs to be much safer than other forms of drugs. For example, according to the Partnership for a Drug-Free America, about 40 percent of youth think prescription pills are safer than “illegal” drugs, and about 30 percent find nothing wrong with using prescription pills to get high. Each day, over 2,500 youth try prescription drugs for non-medical reasons for the first time. The National Institute on Drug Abuse estimates that in 2005, annual abuse of Vicodin was 9.5 percent among high school seniors, making it the most commonly abused drug by that age group. Additionally, OxyContin use has

significantly increased among high school seniors since 2001. The ARC-funded study shows that Appalachian adolescents have a proportionally higher reported rate (10.6 percent) of pill abuse than their counterparts in the rest of the U.S. (8.7 percent).

In a 2008 article in the *Journal of the American Medical Association*, Aron Hall and colleagues report a 550 percent increase in overdose deaths in West Virginia from 2002 to 2006. Their comprehensive review of death records revealed that pharmaceutical diversion (prescription drugs obtained illegally using a variety of methods, including theft, deception, and trade) was associated with 63 percent of deaths, and “doctor shopping” (going to multiple doctors to seek pills) was implicated in more than 20 percent of the cases. The authors also found that 93 percent of those who died had used prescription opioids, and 40 percent had taken methadone, a synthetic, often-abused opioid employed in the treatment of drug addiction. Only 44 percent had a prescription for the drugs they used.

We know where the pills come from—the supply side of the dilemma. They follow a clearly defined and regulated path from manufacturer to shelf. It would seem, then, that the problem could be corrected by clamping down on doctors and pharmacists, training them well, and making sure there is a good system in place to monitor prescriptions and their delivery. Regrettably, it is not that easy.

Around 2001 state-level Prescription Monitoring Programs (PMPs) began emerging in the fight against pill abuse. The presence of a state PMP was touted as a deterrent to diversion. Now, over thirty states have them, and they are providing good information. For example, we know that in 2008 more than 272 million hydrocodone pills were prescribed in Tennessee. That equates to 43.87 pills for each of the state’s 6.2 million residents. We also know that it takes several minutes for a provider to get online and double-check the history of a patient suspected of angling for an illegitimate prescription.

If a provider is legitimate and the attempt to obtain an illegitimate prescription is careful, some pills will wind up in the wrong hands. But the market for pills is not being satisfied by “unwitting” physicians or even a few sloppy clinical care providers. Many pills do come from rogue physicians or “candy-man” doctors, but casual abusers of pain pills acquire most

of their pills from friends or family. Only after a person is pretty highly addicted does he or she begin going to the “candy-man” doctors or the streets. In one survey, more than 58 percent of respondents reported getting prescription drugs from friends or family, and only about 7 percent said they obtained pills from “doctor shopping” or the streets. About 14 percent of callers to the West Virginia Quitline, arguably a more addicted clientele, reported getting their drugs from “doctor shopping” at least sometimes. In the Hall study, some 21 percent of the people who died from overdoses had been “doctor shoppers.” Clearly, as the addiction progresses, the propensity to spend time acquiring the drugs intensifies.

Authorities believe most of the pills now on the street in Appalachia have come up the “pill pipeline” from pain clinics in Florida, resulting in an increase in street-level availability.

### What to do

Prevention of diversion and treatment for pill addiction are desperately needed, but local efforts should be focused on prevention of pill abuse, beginning in the home: Educate yourself about the type of pills you and your family have been prescribed; monitor the exact number of pills that have a psychoactive effect (including pain pills with hydrocodone and oxycodone, sedatives, stimulants, tranquilizers, and many others); secure such pills with lockboxes; and if you have older pills that are potentially risky, put them in an old peanut butter jar, tape the lid shut with duct tape, and put them inside a bag in the trash. Do not flush them down the toilet, since they can wind up in the drinking water down the river or in the water table. Occasionally, pharmacies will hold pill drop-off days when you can dispose of them properly.

In your community, counsel people to monitor their prescription drugs, secure those drugs, and carefully dispose of unused doses. Encourage doctors to use prescription monitoring software. Engage in conversation with friends and family to dispel the myth that prescription drug misuse is safe.

Such measures are necessary to combat the threat that prescription drug abuse poses to our heritage, our culture, and our way of life in Appalachia. ❖